Thyroid Science
An open-access journal for truth in
thyroid science and thyroid clinical practice

A PDF Conversion
of
Dr Lowe’s
Thyroid Science
Website

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A PDF Conversion of Dr Lowe's Thyroid Science Website

15/01/2012

Dr John C Lowe – Sadly Missed

It is with much devastation that Thyroid UK brings you the news that Dr John C Lowe passed away on the 9th January 2012.

Dr Lowe was an inspiration to me and working with him and Tammy has been a wonderful experience. I have many lovely memories of him and I will continue to work for thyroid patients in honour of his work.

The recent communications we have had, have shown how much he thought of Thyroid UK even when he was extremely poorly. A very dedicated and much loved man, he will be sorely missed by Thyroid UK and thyroid patients around the world.

Rest in Peace, John.

Preface

Since Dr Lowe passed away, his website has been only partially available. Many use the WayBack machine (archive.org) in order to access its former content but that has its own problems.

In order to make more accessible the information, this PDF has been created from what remains of Dr Lowe's Thyroid Science website.

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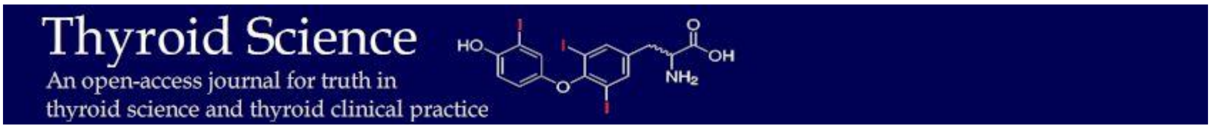
A journal dedicated to truth in thyroid science and thyroid clinical practice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It is also important to realise that the entire content has been left without any updates or corrections for a number of years.

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Case Reports

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We have listed the papers and other written communications below in chronological order from bottom-to-top; that is, latest publications are highest in the list and earliest publications are lowest in the list. —*Dr. John C. Lowe, LLC, Editor-in-Chief*

Padhi, S., Varghese, R.G'B., Ramdas, A., Singh, K., Sahoo, J., Arokiaraj, M.C.: Autoimmune thyroiditis: Correlation of cytomorphology with drug history and clinical implications. *Thyroid Science*, 6(11):CR1-5, 2011.

Jokic, D. and Wang,X.: Primary hypothyroidism associated with hyperprolactinemia and pituitary macroadenoma. *Thyroid Science*, 6(7): CR1-4, 2011.

Joshi, N. and Nag, B.P.: Papillary carcinoma in a thyroglossal duct cyst: A case report, review of literature, and diagnostic pitfalls in fine needle aspiration cytology. *Thyroid Science*, 6(10)CR1-3, 2011.

Najarian, T. and Rosemitt, C.N.: Hypothyroidism, particularly associated with weight loss: Evaluation and treatment based on symptoms and thyroid hormone levels. *Thyroid Science*, 6(6)CR1-3, 2011.

Huang, C., Fresca, D., Jokic, D., and Wang, X.: Development of Postpartum Graves' Hyperthyroidism in a Woman with Hashimoto's Hypothyroidism. *Thyroid Science*, 6(3):1-5, 2011.

Yanai, H. and and Yamazaki, H.: Grave's ophthalmopathy in the absence of abnormal thyroid hormone and thyrotropin levels and thyrotropin receptor antibody. *Thyroid Science*, 6(1):1-3, 2011.

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Lowe, J.C.: Comparative effects of Cynomel and Hypo Support Formula.*Thyroid Science*, 4(10):CR1-8, 2009.

Dunn, M.E., Hennessey, J.V., Cosmas, A.C., Lamont, L.S., and Manfredi, T.G.: Clinical Case Report: Ultrastructural Evidence of Skeletal Muscle Mitochondrial Dysfunction in Patients With Subclinical Hypothyroidism. *Thyroid Science*, 4(6):CLS1-8, 2009.

Colaco, R.J., Menasce, L.P., Ranson, M., Sobrinho Simoes, M., Teijeiro, J.C., Vinjamuri, S., and Yap, B.K.: A clinical case report of cribriform-morular variant of papillary thyroid carcinoma with neuroendocrine differentiation and aggressive behaviour in a patient with familial adenomatous polyposis coli. *Thyroid Science*, 4(3):CR1-3, 2009.

Huang, C., Toscano-Zukor, A., and Wang, X.: Case Report: Hyperthyroidism, Iron-deficiency Anemia, and Celiac Disease. *Thyroid Science*, 4(3):CR1-3, 2009.

Reuben F. De Sousa, MBBS, Amonkar Dilip, MS, FICS, and Correia Mervyn, MS. Thyroid abscess with cutaneous fistula: Case report and review of the literature. *Thyroid Science*, 3(11):CR1-4, 2008.

David M. Derry, MD, PhD: Regeneration of human scar tissue with topical iodine: A preliminary report—part 2. *Thyroid Science,* 3(7):CR1-9, 2008. Contact: dderry@shaw.ca.

Laura Evangelista, MD, Teresa De Falco, MD, T. Carmine di Nuzzo, MD, and Marco Salvatore, MD: Utility of adrhy with ^{131}I-6-β-methyl-norcholesterol in a case of mismatch between morphological and functional PET imaging.*Thyroid Science*, 3(6):CR1-3, 2008.

David M. Derry, MD, PhD: Regeneration of human Scar tissue with topical iodine: A preliminary report—part 1 (three years). *Thyroid Science*, 3(6):CR1-9, 2008.

(*Dr. Derry's report contains multiple high-resolution photos. If the file doesn't open for you, please downloaded the latest version of Adobe Reader. It is available free at the following website and will open the file:* http://www.adobe.com/products/acrobat/readstep2.html.)

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A Clinical Case Report of Cribriform-Morular Variant of Papillary Thyroid Carcinoma with Neuroendocrine Differentiation and Aggressive Behaviour in a Patient with Familial Adenomatous Polyposis Coli

(Full Text Free in pdf format)

R.J. Colaco,[1] L.P. Menasce,[2] M. Ranson,[3] M. Sobrinho Simoes,[4]
J. Cameselle Teijeiro,[5] S. Vinjamuri,[6] and B. K. Yap[1]

1Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK
2Department of Pathology, The Christie NHS Foundation Trust, Manchester, UK
3Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK
4Institute of Molecular Pathology and Immunology, University of Porto and
Department of Pathology, Hospital São João, Porto, Portugal.
5Deparment of Pathology, Clinical University Hospital, Santiago de Compostela, Spain
6Department of Nuclear Medicine, the Royal Liverpool Hospital NHS Trust, Liverpool, UK

Contact: Dr. B. K. Yap Department of Clinical Oncology, Christie Hospital,
Wilmslow Road, Manchester M20 4BX, UK. email: beng.yap@christie.nhs.uk

ABSTRACT. Cribriform-morular variant of papillary thyroid carcinoma (CMVPTC) is a rare variant of papillary thyroid cancer mostly occurring in young females under the age of 30. CMVPTC is associated with familial adenomatous polyposis coli and has an excellent prognosis with most patients surviving upwards of 20 years. We describe the clinical course of an aggressive variant of CMVPTC in a 42-year-old male with the first known reported features of neuroendocrine differentiation (the unusual histological features are published elsewhere in a separate article (Cameselle Teijeiro, J., et al. *Am. J. Clin. Pathol*., 131:134-142, 2009). The patient survived just 23 months from diagnosis and we outline our management here including the use of radiolabelled Yttrium 90 therapy.

Keywords. Cribriform-morular variant • Familial adenomatous polyposis • Neuroendocrine differentiation • Papillary thyroid carcinoma

Colaco, R.J., Menasce, L.P., Ranson, M., Sobrinho Simoes, M., Teijeiro, J.C., Vinjamuri, S., and Yap, B.K.: A clinical case report of cribriform-morular variant of papillary thyroid carcinoma with neuroendocrine differentiation and aggressive behaviour in a patient with familial adenomatous polyposis coli. *Thyroid Science*, 4(3):CR1-3, 2009.

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A Clinical Case Report of Cribriform-Morular Variant of Papillary Thyroid Carcinoma with Neuroendocrine Differentiation and Aggressive Behaviour in a Patient with Familial Adenomatous Polyposis Coli

R.J. Colaco,[1] L.P. Menasce,[2] M. Ranson,[3] M. Sobrinho Simoes,[4] J. Cameselle Teijeiro,[5] S. Vinjamuri,[6] and B. K. Yap[1]

[1]Department of Clinical Oncology, The Christie NHS Foundation Trust, Manchester, UK
[2]Department of Pathology, The Christie NHS Foundation Trust, Manchester, UK
[3]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK
[4]Institute of Molecular Pathology and Immunology, University of Porto and
Department of Pathology, Hospital São João, Porto, Portugal.
[5]Deparment of Pathology, Clinical University Hospital, Santiago de Compostela, Spain
[6]Department of Nuclear Medicine, The Royal Liverpool Hospital NHS Trust, Liverpool, UK

Correspondence: Dr. B. K. Yap Department of Clinical Oncology, Christie Hospital,
Wilmslow Road, Manchester M20 4BX, UK. E-mail: beng.yap@christie.nhs.uk

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Abstract. Cribriform-morular variant of papillary thyroid carcinoma (CMVPTC) is a rare variant of papillary thyroid cancer mostly occurring in young females under the age of 30. CMVPTC is associated with familial adenomatous polyposis coli and has an excellent prognosis with most patients surviving upwards of 20 years. We describe the clinical course of an aggressive variant of CMVPTC in a 42-year-old male with the first known reported features of neuroendocrine differentiation (the unusual histological features are published elsewhere in a separate article (Cameselle Teijeiro, J., et al. *Am. J. Clin. Pathol.*, 131:134-142, 2009). The patient survived just 23 months from diagnosis and we outline our management here including the use of radiolabelled Yttrium 90 therapy.

Keywords. Cribriform-morular variant • Familial adenomatous polyposis • Neuroendocrine differentiation • Papillary thyroid carcinoma

Introduction

Cribriform-morular variant of papillary thyroid carcinoma (CMVPTC) is a rare variant of papillary thyroid cancer that predominantly occurs in young females under the age of 30 and is often associated with familial adenomatous polyposis coli (FAP) and a good prognosis. We describe the clinical course of the first known case in the literature (the unusual histological features of this case having been previously published elsewhere)[1] of an aggressive variant of CMVPTC with features of neuroendocrine differentiation in a 42-year-old male and the subsequent management strategy.

Case History

Whilst undergoing colectomy for his FAP, a 42-year-old man was found peri-operatively to have a thyroid mass. Fine needle aspiration showed features of a papillary carcinoma. As a result he underwent total thyroidectomy and central compartment clearance. He had a familial history of colon carcinoma that affected his maternal grandfather, his mother, 2 of 5 maternal uncles, and 1 cousin. His mother and his only brother also had osteomas.

The right lobe of the thyroid was almost entirely replaced by a solid, fleshy, haemorrhagic yellowish tumour. The histological diagnosis was that of an angioinvasive cribriform-morular variant of papillary carcinoma showing neuroendocrine differentiation. Approximately 40% of the tumour cells expressed chromogranin and synaptophysin. They were negative for calcitonin and thyroglobulin. Molecular studies showed germline and somatic APC gene mutations as well as RET/PTC rearrangement but no BRAF, nor RAS mutations were found. Seven lymph nodes were resected and all were free of tumour. Inflamed diverticuli were found in the colectomy specimen but no adenomatous polyps were present. The unusual histological features of this case were published in more detail in a separate article by Cameselle-Teijeiro, et al.[1]

Staging thoracic CT scan showed bilateral pulmonary metastases without any clinical symptoms. The patient's serum thyroglobulin was undetectable without thyroglobulin antibodies. Six months following initial diagnosis, he developed multiple brain metastases and right neck nodal metastasis. His brain metastases were treated with palliative whole brain radiotherapy. He was considered for radio-labelled ocreotide therapy in view of the presence of neuroendocrine differentiation in the tumour. Ocreotide-111Indium scan showed significant uptake in the right neck and lungs. He was treated with 5 GBq of dotatoc-^{90}Yttrium.

The patient had a good clinical response with significant reduction in the size of the metastatic mass in the right neck. The duration of his good response however, proved to be short-lived, as a CT scan 4 months post dotatoc therapy showed progressive disease. He underwent a further 5 GBq of dotatoc-^{90}Yttrium therapy with significant uptake in the neck lesion but no uptake in the lung and brain metastases. He died 6 months after his second dotatoc-^{90}Yttrium therapy, having survived just 23 months from the time of diagnosis.

Discussion

Thyroid carcinoma as an extra-intestinal manifestation of FAP has been well documented. The prevalence is thought to be as high as 12%.[2] The adenomatous polyposis coli (APC) gene plays an important role in the development of cribriform-morular variant of papillary thyroid carcinoma.[3] The CMVPTC is a rare variant of thyroid cancer with an estimated prevalence of 0.16% of all papillary thyroid cancers and is usually associated with a good prognosis.[4]

Both conventional PTC and CMVPTC associated with FAP predominantly occur in females under the age of 30 and are usually multi-focal. CMVPTC tends to behave in a similar manner to conventional papillary thyroid carcinoma; Cameselle-Teijeiro, et al. published seven of nine cases reported to be alive and completely disease free 1-13 years after follow up.[5] Most patients with FAP associated PTC survive long term with survival rates of up to 77% at 20 years.[6] In contrast our 42 year old male patient had an aggressive disease course and survived only 23 months.

The unusual features present in this case (i.e. high nuclear atypia, high mitotic activity, high proliferation index, marked angioinvasion, neuroendocrine differentiation, overexpression of cyclin D1 and strong expression of P53) suggested a "less-differentiated" (poorly differentiated) CMVPTC.[1] These features correlated well with the aggressive course of disease seen in this case.

Most reported cases of CMVPTC usually involve encapsulated or locally advanced tumours without distant spread. The usual treatment of such cases consists of total/near total thyroidectomy with or without radioiodine therapy.

The principal reasons for pursuing dotatoc therapy in this case were the advanced nature of the disease and the neuroendocrine component of the tumour with negative staining for thyroglobulin; radioiodine treatment would likely have been ineffective. The MAURITIUS study[7] showed evidence of a 56% response rate (either regression or stable disease) following treatment with 1 to 4 doses. There were no episodes of serious adverse events reported.

Most papillary thyroid carcinomas are associated with one of two mutations: RET/PTC rearrangement and BRAF mutations. Accordingly, our patient was considered for Sorafenib which is known to target cell signaling mechanisms involving VEGF and BRAF, and which has been evaluated in phase 2 studies in advanced thyroid cancers.[8] However, given the absence of BRAF mutation, this therapeutic avenue was not pursued.

Conclusions

We describe additional information about the first case of CMVPTC showing neuroendocrine differentiation in a patient with FAP associated with other striking features including the atypical age, gender and aggressiveness of disease. In spite of our patient's final outcome, based on the increasing knowledge of the molecular pathophysiology of thyroid cancers, clinicians should consider novel therapies as one potential therapeutic option when faced with treating rare tumours of this nature.

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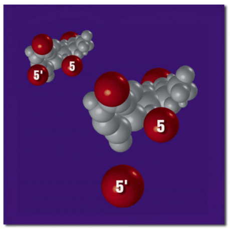

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Thyroid Abscess with Cutaneous Fistula: Case Report and Review of the Literature

(Full Text Free in pdf format)

Reuben F. De Sousa, MBBS, Amonkar Dilip, MS, FICS,
and Correia Mervyn, MS

Department of Surgery, Goa Medical College; Goa, India

Contact: Dr. Reuben De Sousa, Room 45, GARD Hostel, Bambolim-Tiswadi-Goa, 403202
+91-9423810573 reuben_ds@yahoo.co.in

ABSTRACT. Thyroid abscess arising as a complication of nodular goiter is a rarely documented phenomenon. Acute suppurative thyroiditis is usually associated with pyriform sinus fistula in children, whereas in adults the cause is usually disseminated infection. A good response is noted to drainage and excision with antibiotic cover. We report the case of an adult female who presented with a longstanding multinodular goiter with recent onset of inflammation and a discharging external fistula. The causative organism was Staphylococcus aureus. The patient staged an uneventful recovery following hemithyroidectomy with fistulectomy and intravenous antibiotics.

Keywords. Multinodular goiter • Thyroid abscess • Thyroiditis

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Thyroid Abscess with Cutaneous Fistula: Case Report and Review of the Literature

Reuben F. De Sousa, MBBS, Amonkar Dilip, MS, FICS, and Correia Mervyn, MS

Department of Surgery, Goa Medical College; Goa, India

Contact: Dr. Reuben De Sousa, Room 45, GARD Hostel, Bambolim-Tiswadi-Goa, 403202
+91-9423810573 reuben_ds@yahoo.co.in

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Abstract. Thyroid abscess arising as a complication of nodular goiter is a rarely documented phenomenon. Acute suppurative thyroiditis is usually associated with pyriform sinus fistula in children, whereas in adults the cause is usually disseminated infection. A good response is noted to drainage and excision with antibiotic cover. We report the case of an adult female who presented with a longstanding multinodular goiter with recent onset of inflammation and a discharging external fistula. The causative organism was Staphylococcus aureus. The patient staged an uneventful recovery following hemithyroidectomy with fistulectomy and intravenous antibiotics.

Keywords. Multinodular goiter ● Thyroid abscess ● Thyroiditis

Introduction

Acute suppurative thyroiditis is an uncommon condition. A review of the literature from the years 1900-to-1980 turned up only 224 cases, the majority of which were reported in children with predisposing factors such as pyriform fistula or thyroglossal duct.[1]

Pre-existing thyroid diseases, including longstanding thyroid goiter and thyroid malignancy, are known predisposing factors. Organisms commonly responsible for bacterial thyroiditis are those that typically colonize the skin and oropharynx. However, mycobacteria, fungi, and gram-negative rods have also been documented.[2]

Suppurative thyroiditis must be considered in the differential diagnosis of stridor. Untreated cases may lead to septicaemia, osteomyelitis, or septic thrombophlebitis. Early biopsy and cultures are needed for prompt antimicrobial therapy. Surgical drainage is required for large abscesses.[2]

We report the case of a 60-year-old female with an endemic multinodular goiter. She presented with acute suppurative thyroiditis and a discharging external fistula along with sick-euthyroid syndrome.

Case History

A 60-year-old female (S.D., a farmer by occupation) originally from Uttar Pradesh state of North India was admitted with complaints of a swelling in the anterior portion of her neck with overlying ulceration. The swelling had been present for the last 33 years, following her first pregnancy, and had since slowly increased in size (see Figure 1). She had a history of palpitations and being easily fatigued. The patient had developed hoarseness of voice and difficulty in swallowing over two months. She said she also had skin discoloration over two months and described rupture of the swelling with purulent discharge for one week. She had no history of neck irradiation, foreign body impaction, respiratory tract infection, or contact with tuberculosis. The patient's sister-in-law was also suffering from a goiter and had a history of dietary intake of iodine-deficient rock salt.

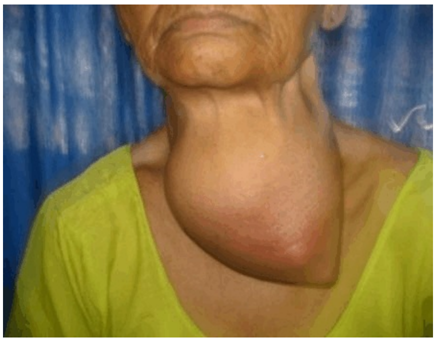

Figure 1. Multinodular goiter with a pointing thyroid abscess.

Vitals on admission showed a blood pressure of 130/72 mm Hg, heart rate of 86 beats/min, respiratory rate of 20/min, and oral temperature of 36.7°C (98.06°F). She was thinly built, alert, and appeared uncomfortable. Her thyroid gland was enlarged to a dimension of 16 x 15 cm. It had a 1 x 1 cm overlying ulcer on the upper left side with purulent discharge. The left side of the gland was predominantly enlarged, tense, tender and cystic, without bruit, pushing the trachea to the right. The skin that overlay the goiter was erythematous, but no engorged veins or lymphadenopathy was present. Swallowing exacerbated her pain. Her sleeping pulse rate was normal (70 beats/min). Deep tendon reflexes were slowed and no tremors were present.

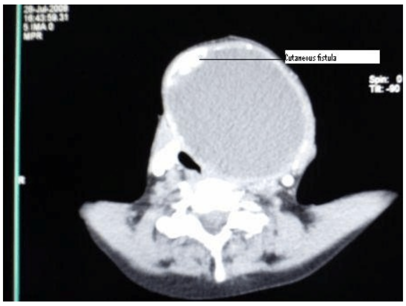

Figure 2. Thyroid showing large hypodense nodule.

Figure 2 is a thyroid CT scan showing a large hypodense nodule with peripheral enhancement and cutaneous fistula. Laboratory studies showed hemoglobin of 11.5 g/dL, white blood cell count of 8900/µL, and erythrocyte sedimentation rate of 35mm/hour. Thyroid function tests showed low T_3 (<5.0 ng/dL), low T_4 (<3.0 µg/dL), and a reference range TSH (3.6 µU/mL), suggestive of euthyroid sick syndrome. ECG revealed left bundle branch block and poor R wave progression. X-ray of the soft tissues of the neck showed tracheal compression by a homogenous soft tissue density pushing it to the right. The retropharyngeal space was normal.

Thyroid ultrasonography revealed that the left lobe of the thyroid gland was enlarged. The lobe had multiple enlarged cystic lesions with dense internal echoes and a peripheral rim of coarse calcification. CT scan of the neck and thorax showed that the left lobe of the gland was replaced by multiple nodules. The largest nodule measured 9 x 10 x 9.3 cm, with peripheral rim enhancement and foci of coarse calcifications in the wall. The patient's trachea was deviated to the right. Indirect laryngoscopy was normal with no evidence of pyriform sinus or cord abnormalities. Needle aspiration yielded yellow-brown pus—hence the patient was commenced on broad spectrum antibiotics and IV fluids and scheduled for surgery.

The enlargement of the left lobe of the gland was 15 x 15 cm and was, again, cystic in consistency. The overlying ulcerated skin was excised *in toto*. The cyst was incised and about 500 mL of purulent fluid was drained. Following this, left hemithyroidectomy was performed.

Figure 3 shows a gross specimen of hemithyroidectomy (cut open) with areas of calcification. In view of the tracheal compression, delayed extubation was performed after 24 hours. The patient was conscious and afebrile on post-op day one and was breathing room air. She staged an uneventful recovery and was discharged on post-op day five.

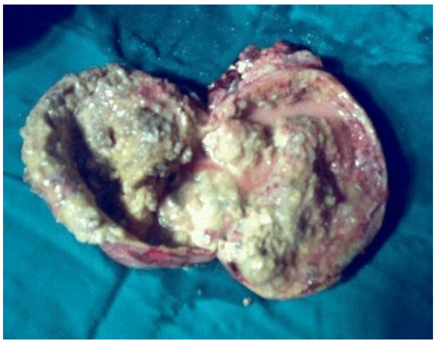

Figure 3. Gross specimen from hemithyroidectomy cut open and showing calcification.

Pus culture showed methicillin-resistant Staphylococcus aureus sensitive to vancomycin and teicoplanin. Histopathology of the abscess wall revealed dense fibrous tissue, necrosis, cholesterol clefts, and foreign body giant cells with spindle cells in areas of fibrosis. The surrounding thyroid gland showed colloid goiter. Due to the large areas of necrosis and spindle cells, immunohistochemistry was performed to rule out anaplastic carcinoma; tests for thyroglobulin and cytokeratin were negative.

At one month post-op, the patient had a healthy scar with no noticeable complications. Hoarseness and dysphagia had resolved and thyroid function tests showed reference range values: her T_3 was 86.0 ng/dL, T_4 was 5.62 µg/dL, and her TSH was 6.97

μU/mL. The patient did not require thyroxine or calcium supplementation.

Discussion

Thyroid abscess and acute suppurative thyroiditis are not common, representing only 0.1%-to-0.7% of surgically treated thyroid pathologies.[3] More common in children than adults, these rarities are associated with poorly indicative clinical symptoms, thus making diagnosis difficult. In a literature review in 1981, Schweitzer and Olson noted that only 39 cases of thyroid abscess had been reported in the medical literature since 1950. Of the 39 cases of abscess, 16 were in children.[4]

Infections of the thyroid gland are rare due to its isolated anatomic location, fibrous capsule, rich blood supply, generous lymphatic drainage, and high content of iodine. An infection may result from hematogenous or lymphatic seeding, or may spread directly from the oropharynx, contiguous cervical tissue, esophageal perforation, foreign bodies, or patent thyroglossal fistula.[2]

More than two-thirds of the women and half of the men with acute suppurative thyroiditis have preexisting thyroid disease.[5] In a study by Nmadu in Nigeria, 14 of 17 cases of thyroid abscess had preexisting multinodular goiter.[6] In another study by Nmadu, Ameh, and Sabo in Zaria-Nigeria, the incidence of thyroid abscess developing in endemic multinodular goiter was 10.7% over ten years (9 of 84 cases).[7]

In 1978, Takai et al. reported 15 patients with acute suppurative thyroiditis in whom a pyriform sinus fistula was the apparent source of infection.[8] The fistula originates from the pyriform sinus, and ends blindly in the parenchyma of the thyroid gland or in the perithyroid soft tissue. The fistula tends to become infected after a bout of upper respiratory tract infection that is attributed to the accumulation of contaminated secretions in the pharynx and fistulous tract. Presentation is usually as a left-sided neck mass which can cause overlying skin erythema as it enlarges. After diagnosis by barium esophagography and computed tomography, treatment involves antibiotics, drainage, and fistulectomy.[9]

The most important causal organisms are Staphylococcus aureus, Streptococcus species, and anaerobes. These infections account for approximately 70% of cases.[10] Other causes include Escherichia coli following urosepsis,[2][10] Bacteroides fragilis in post-hysterectomy,[11] Klebsiella, Salmonella typhi, Salmonella brandenburg, Eikenella corrodens, Fusobacterium mortiferum,[12] and aspergillosis.[13] Rare cases have been reported from Lemierre's syndrome[14] (post-anginal septicaemia due to anaerobes) and infectious mononucleosis in adolescence[15] presenting with thyroid abscess.

Acute suppurative thyroiditis responds well to intravenous antibiotics with or without incision and drainage of the abscess. The condition rarely causes an external fistula.[8] In our case, a decision to perform a partial thyroidectomy was made in view of a large abscess in the left lobe which must have burst through the perithyroidal tissues to involve the skin. The external fistula was treated by fistulectomy and primary closure. The patient's dysphagia and hoarseness of voice improved rapidly following the surgery, and the euthyroid sick syndrome rapidly resolved postop.

In conclusion, acute suppurative thyroiditis is a little known complication of multinodular goiter. It usually results from concomitant sepsis or anatomic abnormality such as pyriform sinus. Management must integrate the treatment for possible abnormal thyroid status with the treatment of sepsis and removal of the causative anomaly.

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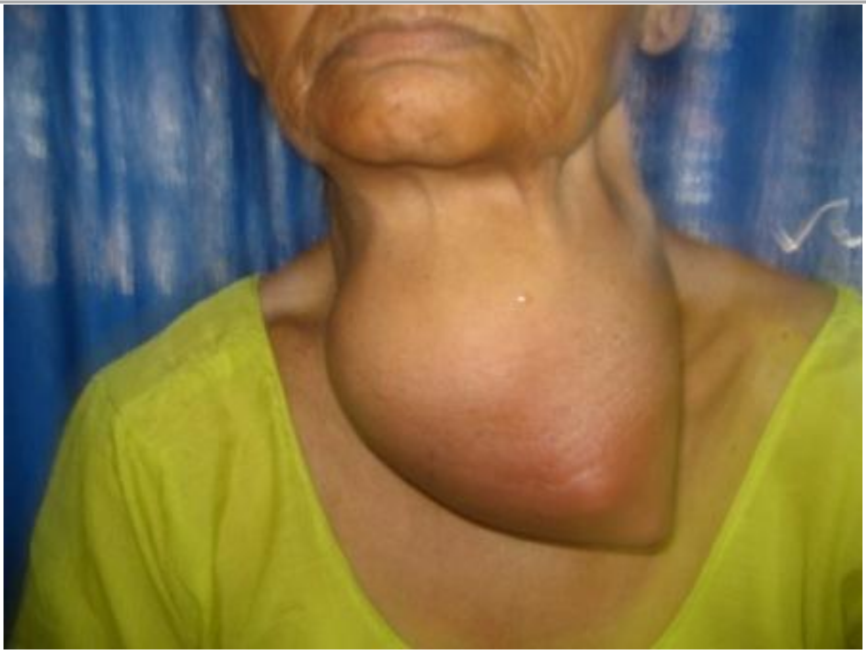

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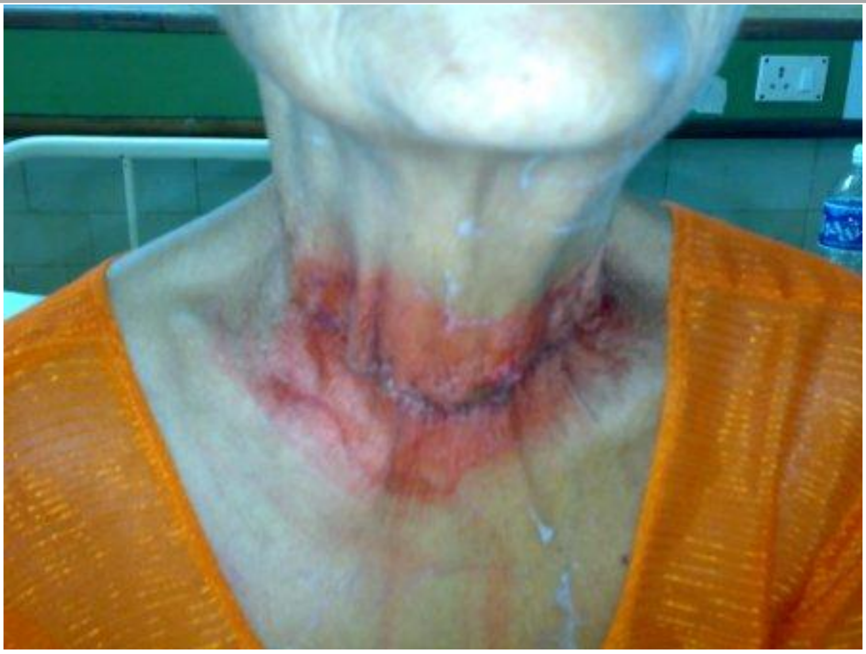

Postop photograph of patient provided by
Dr. Reuben F. De Sousa as followup to case report.

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Thyroid Science 3(6):CR1-9, 2008 www.ThyroidScience.com *Case Report*

Regeneration of Human Scar Tissue with Topical Iodine: A Preliminary Report—Part 1 (Three Years)

David M. Derry, MD, PhD*

*332-425 Simcoe Street, Victoria B.C. Canada, V8V 4T3
Contact: dderry@shaw.ca

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Abstract. Since Spallanzini first described salamander limb regeneration in 1769, there has been slow progress in understanding this process. Potential treatment benefits from regeneration are worth the effort. A hypothesis that topical iodine would regenerate human scar tissue is tested by applying Lugol's solution to four scars of various sizes, degree of damage, and location for variable lengths of time. Regeneration starts a few days after applying iodine and stops and forms adult scar if applications are discontinued. One face scar has completely regenerated. The wrist scar's terminal stages are being studied. The remaining two scars on the abdomen are behaving as if they are one and could take considerably longer to complete. Waiting for completion delays availability of this information for scientists, physicians, and patients.

For the past three years, Nikon Cool Pix cameras recorded regeneration changes. Regenate material found under plastic wraps on the scars comes in two forms, snow-like and globular. Their function is unknown. Two black dots both 5 mm apart seen on the wrist and abdominal scar store iodine and appear to coordinate regeneration. Hair is the regeneration workhorse and does an amazing number of things. Amongst the hair activities are free movement to any cell within its range in any direction and self-amputation possibly to strengthen regenerating tissue. Hair delivers regenate material and may be sending cell signals by touch, regenate material, and electrical impulses. The hypothesis that topical iodine in the form of Lugol's solution regenerates human scar tissue back to normal is supported by these preliminary findings.

Keywords: Hair • Hair movement • Iodine • Regeneration • Scars • Self-amputation • Skin • Wound healing

Introduction

Regeneration and Wound Healing

Spallanzini in 1769 and Martin 230 years later expressed the same hope that a way is found to regenerate human tissue damage back to normal.[1][2] Unfortunately, we are not yet close to unraveling either regeneration or wound healing. We do not understand regeneration and progress is limited.[1] Wound healing is also complex.[15] Cotran says, "The magic behind the seemingly precise orchestration of these events (wound healing) under normal conditions remains beyond our grasp. . . ."[3, p.109] On the other hand, Tsoni says, "The field of limb regeneration will prove to be one of the most important in the biomedical field."[23, p.203]

Iodine

Elemental iodine discovered in 1812 by Courtois has been a universal antiseptic for 150 years,[4] and its only established human body function is making thyroid hormones in thyroid glands from dietary iodine. Long term iodine intake levels dictate thyroid gland function and pathology. Iodine is found in every body cell and fluid.[5][6][7] In relation to regeneration, thyroidectomy makes it abnormal and excess thyroid hormone inhibits it.[1][8, p.149]

In 1997 while treating patients with Lugol's iodine for fibrocystic disease,[9][10] out of curiosity, the author applied Lugol's solution to a 50-year-old face scar that resulted from removal of a birth mole. Topical applications for three consecutive days did nothing. On the fourth day, the thin 2 cm white scar became red and hyperemic. Could this be regeneration? A hypothesis was formed: topical iodine in Lugol's form could regenerate human scar tissue back to normal. Eight years later, the author began iodine applications to test this hypothesis.

Materials and Methods

Lugol's Solution

Lugol's solution is made of 5% free iodine and 10% potassium iodide in water. Free iodine (elemental iodine) is only slightly soluble in water, but 200 years ago Henri Lugol, a Paris physician, discovered that potassium iodide increased free iodine's solubility in water. Three chemical iodine species exist in Lugol's solutions: free elemental iodine, triiodide, and iodide.[11][12][13] Free iodine reacts with water to make Lugol's solution brown, triiodide's weaker yellow color is not visible, and iodide is colorless.[4]

Four Scars

During the 8 years between Lugol's solution scar applications, the author gained three new scars: two abdominal and one on the left wrist. (Figures 1 and 2.) An 18cm vertical abdominal scar was opened three times and accompanied by a horizontal colostomy scar. If we include the old one, there are four scars to study.

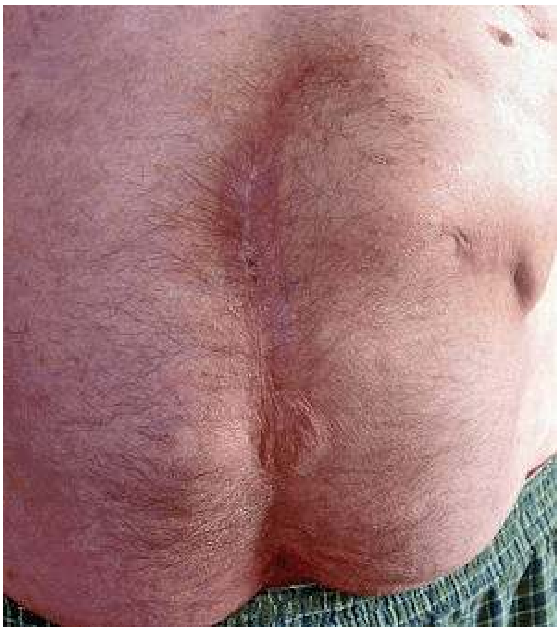

Figure 1. Photo of 18 cm abdominal scar which was opened three times. Note the abundance of hair growth, induced by iodine, around the scar. The two black dots are the coordinating centers (5mm apart) and are level with the colostomy scar seen on the right of the picture (left of the abdomen). The umbilicus disappeared for two months and reappeared in this form. Note that applications of iodine have been stopped, and the scars have reverted to the adult form. The coordinating centers have stayed in place.

Best Method of Iodine Application

After medical discharge, Lugol's solution applied topically to scars began regeneration within several days. Daily scar application of iodine and covering with plastic to retain moisture and prevent iodine evaporation worked best.

Documentation with Cameras

Scar regeneration monitoring with normal microscopic procedures is impossible. Several small Nikon Cool Pix cameras with 5-to-8 mega pixels recorded changes. A zoom lens and one camera with an enlarging attachment enabled magnifications of 3-to-20 times.

Photographing in order to learn what changes were occurring is unusual because there is no way of telling what you will find. New findings, stumbled upon, were automatically recorded. These findings were followed-up with a time-lapse photographic approach. Watching the regenerating area with a magnifying glass was like watching clouds—slow, and not helpful.

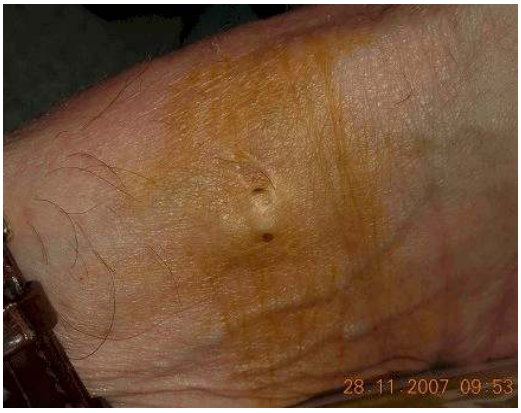

Figure 2. Wrist coordinating centers. They are dark because of the uptake of iodine for storage. They are 5mm apart. A partial trace of the residual scar in white is seen above the upper center. These two centers stayed in place during regeneration. This picture is taken 1.5 years after starting applications. The iodine stain is easily seen.

Results

Definitions of Regeneration Terms, Free Iodine, and Skin Behavior

Coordination Centers

As long as iodine is applied daily with a plastic cover, regeneration continues. Over three years of study, no two pictures of any scar are the same even when the second is taken only a few minutes later than the first. Two dots 5mm apart appeared on both wrist and abdominal scars. The dots seem to coordinate tissue activities and are named coordinating centers. (Figures 1 and 2.)

Regenate Material: Two Types

White Regenate Material. While under plastic wrap, a snow-like substance named white regenate material fell like snow onto scars, producing flat white layers. As topical iodine application levels increased progressively, the white regenate material became yellow, green, light brown, and then brown. Without plastic wrapping, regeneration was considerably slower and much less interesting photographically, and exhibited few signs of either kind of regenate material.

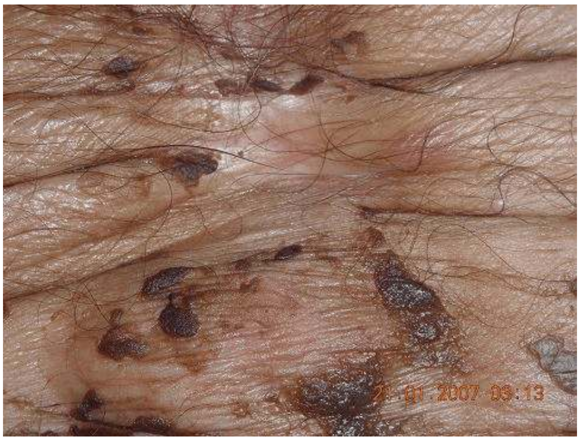

Figure 3. Abdominal scar below the umbilicus. A number of globular regenerating masses are shown clearly soon after removing the plastic wrap. There is no special shape or size. The dark color likely is stored iodine. Abundant hair is intimately involved with every aspect of regeneration. Some sense of the finger-like swellings that continuously bind the two sides together can be seen on both sides. The large round non-descript area at the bottom of the photograph is the partially formed umbilical hernia.

Globular (Masses) Regenate Material. Under plastic wrap—once regeneration was well under way—globular non-descript masses appeared on scar areas on both abdominal and wrist scars. These globular masses had no standard shape or size and changed shape frequently. Most globular masses had hair associated with them. (Figures 3 and 4.)

Free Iodine's Behavior on Skin

Lugol's free iodine stains skin brown and evaporates rapidly. A stain loses 50% free iodine within two hours, 80% within two days, and by the third day 88% has evaporated. No further evaporation takes place. Therefore 12% of any one application gets into skin tissues as iodide. Covering with plastic minimizes evaporation and helps the regeneration rate. Iodide is also soluble in skin and would add to tissue levels.[12][21]

Skin Response to Excess Iodine Application

If iodine applications were excessive especially on skin and not the scar, slight stinging resulted for a few minutes. This caused no ill effects, but may be a tissue signaling that iodine is not needed at that site, time, and dosage. Scars and scabs were much more iodine tolerant. Skin removes excess iodine triggering a few surface cell deaths (apoptosis).[10] These dying cells in turn release more proteins for iodine to react with. This more heavily-stained dead tissue sloughs off, but when under wrap it recycles into regenerating scar.

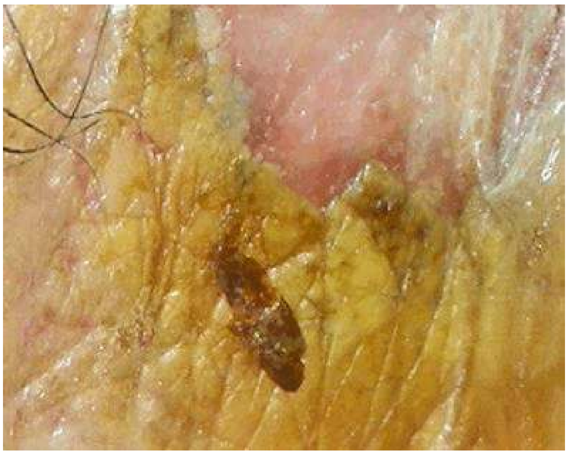

Figure 4. Wrist globular mass (regenerating material) as seen through plastic wrap. There is yellow regenerating material (white with iodine in it). It was difficult to tell if globular mass shape changes or small movements were artifacts of body movement. Abdominal globular masses were mostly 5-10mm in size, and wrist masses 1-2mm. This mass is about 3mm long. It changed direction many times but did not move. It lasted about 2 days and then disappeared.

Wrist Scar Details

The wrist scar was a source of detail because it was easy to photograph. Two weeks post injury the wound became infected. Antiseptic iodine applications cleared the infection. When the scab fell off, in the middle of the 2cm scar were two dark dots 5mm apart straddling the radial artery. In retrospect, these two dots indicate that regeneration starts during antiseptic iodine applications. The dots remain in place during regeneration (3 years). Time-lapse photography suggests that they coordinate regeneration. During regeneration, it appears as if everything moved except coordinating centers and hair follicles. Wrist coordinating centers were composed of one cell storing iodine. The centers continuously changed appearance within two minutes—for three years. There was also a palpable subcutaneous ridge between the wrist centers (this did not happen with the abdominal scar).

Because nearby wrist hair interfered with photographing the coordinating centers, only once—early in the process—were hairs shaved away. Better coordinating center pictures resulted, but the shaving slowed regeneration. As we learn below, hair is a regeneration workhorse.

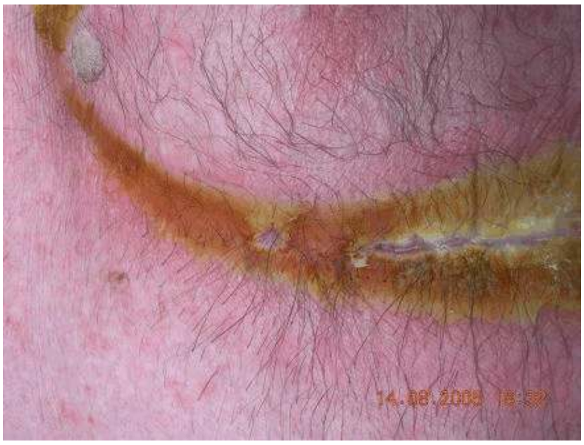

Figure 5. This is a picture of the top of the abdominal scar about a month after starting applications of iodine. Note the large number of new hairs adjacent to and in the crevasse. At the end of the crevasse there is a tiny black dot. This was the first sign of the coordinating centers for the abdominal scars.

Face Scar Regeneration

The face scar was the easiest to regenerate. No coordinating centers appeared at any time. As surgery was done by a plastic surgeon, there was minimal tissue damage and it was gone in 6 months.

Abdominal Scars (Laparotomy X3 and Colostomy)

During the initial healing process, the scar below the umbilicus had an obvious tissue deficit and thus was healing with secondary intention. Whereas, above the umbilicus scar edges were apposed and healing was by primary intention.

The two scar areas above and below regenerated differently. At any time, either the upper or the lower half of the scar was active while the other half was quiet. The halves switched roles at about 6-month intervals. The top half scar formed crevasses with abundant regenerate material and hair. (Figures 5 and 6.)

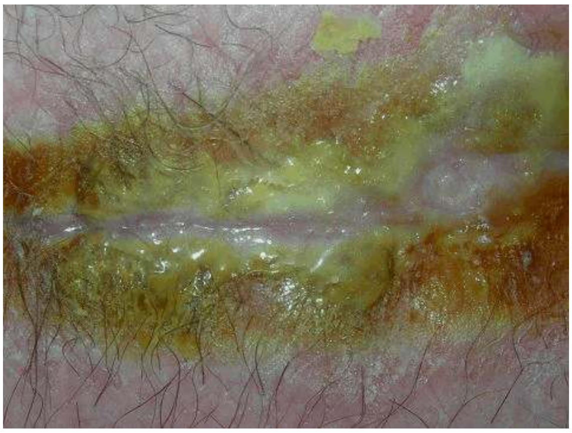

Figure 6. This picture is also of the upper part of the scar closer to the umbilicus. The umbilicus is the round white mass on the right hand side. The umbilicus was on its way to disappearing at this point. There is abundant regenerate material and hair around the central crevasse. Picture is taken through a plastic wrap. In the middle, some regenerate material can be seen sticking to the plastic wrap. More of a brown color regenerate material is sticking to the wrap on the lower left side of the scar. The white glistening is an artifact from the wrap.

Below the umbilicus regeneration was interesting. The two scar sides had a significant deficit gap. The walls approached each other acting somewhat like two hands with fingers extended pointing at each other as they came together. (Figure 3.) One or more “fingers” on one side would slide over the gap and attach to the other side. Then the opposite side would do the same thing. These swellings (like fingers of the hand) just welled up from tissues, and might not take longer than a couple of hours to cross over and complete. The (finger-like) swellings were thick until later stages of regeneration, when they thinned. This went on for years.

Three Hernias: Umbilical, Left Side Abdominal, and Colostomy Muscle

The umbilicus exhibited various appearances during the first year. At one point the umbilicus disappeared. A couple of months later umbilical tissue reappeared (Figure 1), and a year later it formed an umbilical hernia to aid regeneration.

Two Other Hernias. Two other hernias, one a small abdominal hernia opposite the umbilicus and another, a colostomy muscle hernia, moved medially (each towards the middle) towards and began merging with the umbilical hernia. In Figure 1 where the scar has been regenerating for over a year, there is still no sign of either the abdominal hernia or the colostomy hernia (which become prominent a year or so later).

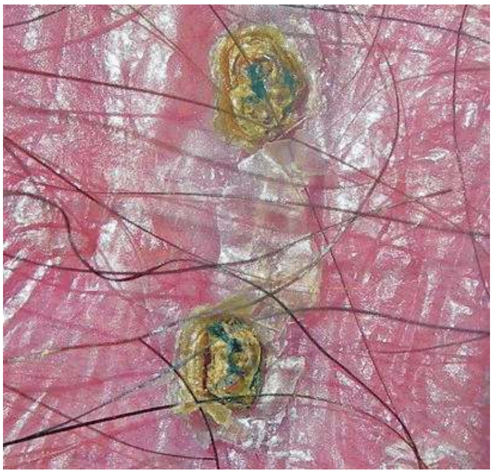

Figure 7. The two abdominal coordinating centers in one of their many types of appearances. Viewing on the back camera screen, it was easier to see that they were made of numerous cells. It was not possible at the time to capture this impression. The multicolor is real; no artificial stains except for iodine have been applied. In most cases, each color represented a different cell. Remember that everything in the picture is alive, even hair—when viewed as a functional follicular unit.

Abdominal Coordination Centers

For about a year there were two much larger coordinating centers centrally placed on the big scar 5mm apart and consisting of more than 50 cells. (Figures 1, 5, and 7.)

Wrist centers remained in place from beginning to end. Each center in both pairs was independent and acted differently. The wrist centers had a palpable subcutaneous ridge between them while the abdominal centers had no such connection. Both pairs of centers took up iodine avidly after staining, and stored it.

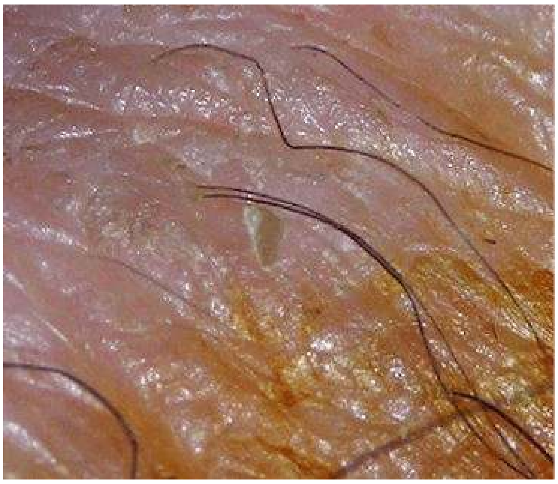

Figure 8. This is not hair #1, but the image shows the same type of kink that hair #1 did just prior to self-amputating at the kink site. A pair of hairs in the foreground emanate from the same follicle.

Hair (Workhorse of Regeneration): Hair Types

Hair activities were central to regenerating scars. Time-lapse photography helped tease out details of hair's multiple activities. There are many types of hairs such as long, short, small, fine, thick, flat, and occasionally hollow. Hairs occur sometimes in groups of two or three. This is a summary of some of the findings on hair activities.

Some of Hair's Activities:

- Hairs on their own move accurately to any cell location within reach in all directions. Sometimes wrist movement aided the hair movement.
- Hair movements were by short rapid jerks.
- Self-amputation is a repeating continuous property of hair in regenerating tissue.
- Hair stubs with follicle, after complete self- amputation, may disappear completely for weeks and then reappear and grow back.

- Hair carried regenate material to cells, coordinating centers, and to tissues in general.
- Hair follicles appeared to be the source of white regenerating material.

Hair cell and tissue signaling:

- Hair may have multiple methods of cell signaling such as touch, electrical, regenate material, and inter-hair communications.

Hair Study Methods and Hair Movement.

Wrist field hairs were numbered. Hair #1 is flat, making direction changes easier. (Figures 8-12.) All hairs are capable of moving on their own in short rapid jerks. Wrist movement aids hair movement sometimes. Destination changes occur as many as 6 times per day and more at night. Only once did the author see hair #1 move. Staring at the hairs for an hour was useless and mind-numbing.

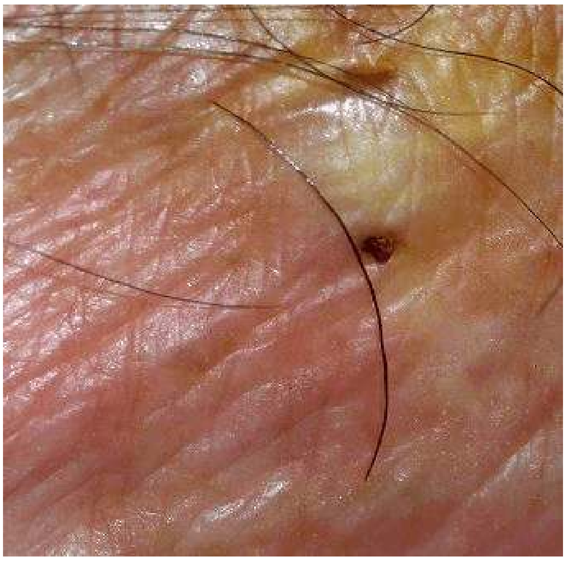

Figure 9. A photograph of hair #1 down the center with some regenate material on it. This is about b its actual size. The two coordinating centers are easily seen and present in a multitude of different forms all the way through regeneration. They are 5mm apart and there is a firm palpable subcutaneous ridge between the two centers not visible in this picture.

Hairs also went to new destinations by rising up above skin vertically and then coming down at their destinations an hour or two later. These destinations appear to be exact, as the hairs return to the same spots numerous times. All these movements may be controlled by iodine, but arrector pili muscles near hair follicles also cause moving.[14, p.355]

Source of Snow-Like Regenate Material.

In the first year it took many photographs to arrive at the conclusion that white regenate material forms in follicles and then transports up the hair. The mechanism of regenate material movement on hair is unknown. Most times white material is flat on the hair. The white material on hairs is discontinuous, raising the possibility of coding by another signaling system.

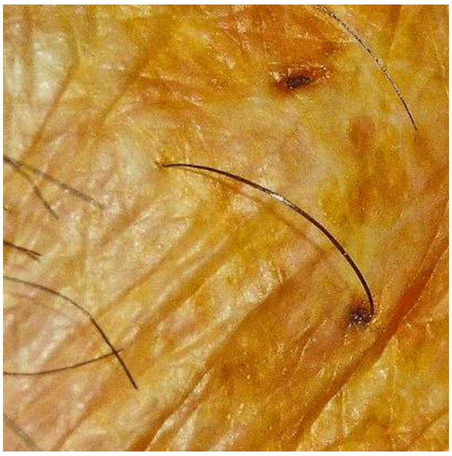

Figure 10. Photograph of hair #1 and the two wrist coordinating centers. Hair #1 is delivering regenate material to the coordination center on the ulnar side of the wrist. Hair #1 is shortened even further in this picture. Regenate material can be seen on hair #1 and around the other coordinating center. Discontinuous regenate material shows on the hair curving over the top coordinating center in an almost code-like manner. The thinness of hair #1 near the follicle is related to this hair’s flatness. Depending upon how the hair is photographed along its length, it can go back and forth between thick and thin.

Hair Self-Amputation Multiple Methods.

While watching hair #1, a kink formed about ¼ of the way up the hair from the follicle to the point the kink touched skin. (Figure 8.) Within a few hours hair #1 self-amputated at that point. The cut-off hair end sank into regenerating tissues. The proximal short hair end continued as if nothing had happened, sending regenate material to nearby tissues. About a week later hair #1 self-amputated again near the follicle leaving only a short stub. (Figure 12.)

Then, approximately a month later, hair #1 regrew again to normal size. On two occasions stub and follicle disappeared completely only to return again several weeks later. Self-amputation is a general hair phenomenon during regeneration. (Figure 12.)

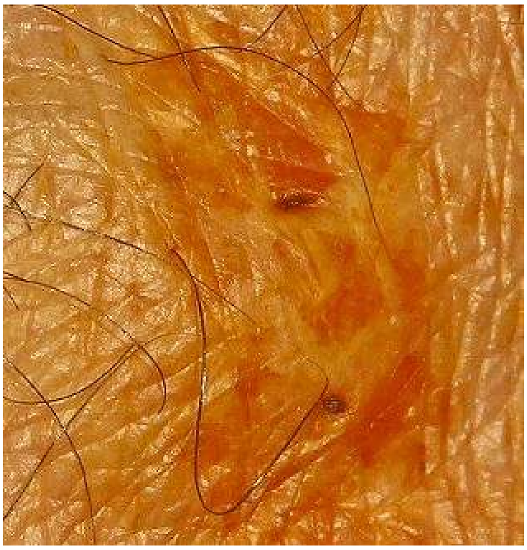

Figure 11. Hair #1 making contorted moves, when it is longer, to deliver regenate material and/or signals to the lower center area. It's length is considerably longer than in the previous photograph. There are two small areas of regenate material on hair #1. Other hairs also show white regenate material.

Oral Iodine and Regeneration

Oral iodine had no detectable influence on regeneration. Even high doses did not stop adult scar formation when topical iodine was discontinued.

What About Controls?

Normal controls were not possible. Multiple scars of different types, sizes, and severities—along with stopping and starting regeneration numerous times for variable periods—provided the only possible controls.

Discussion

The Hypothesis

The results of this case report support a hypothesis: Topical iodine in the form of Lugol's solution regenerates human scar tissue back to normal. Checks of result validity were put into methods and results. The procedure, as described, is harmless. So, physicians, scientists, and patients (with their physicians) can examine regeneration themselves. Regeneration is both unbelievably marvelous and at the same time mysterious because so many questions arise as it progresses.

Total Time of Regeneration

Because abdominal and colostomy scars act as if they are one big scar, when considered together, regeneration may take longer. Waiting for completion seems unnecessary. Regeneration attended to properly without stopping should be considerably faster. But as this was an exploratory experiment and there was no hurry, stopping and starting regeneration was repeated many times, sometimes for as long as 4 months.

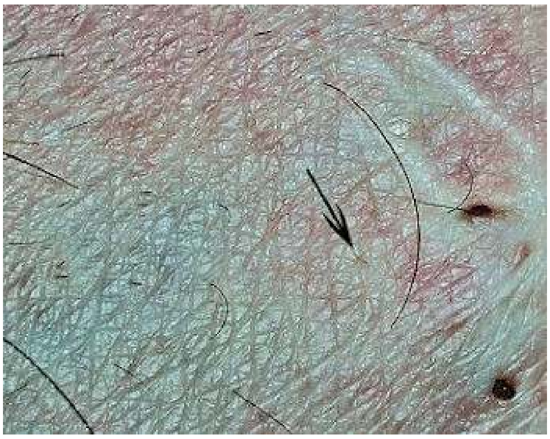

Figure 12. Picture of wrist regenerating area (radial artery runs under this area and between the two coordinating centers). The hand is to the right of the picture. The arrow points to what is left of the stub of hair #1. Including hair #1, there are 15 hair stubs in this picture. This illustrates the magnitude of hair self-amputation.

Two Types of Regenate Materials (Snow-Like and Globular Mass Type)

A by-product of regeneration is regenate material. There are likely more unidentified regenate materials. Because of their reactions with iodine (changing color), regenate materials may turn out to be a host of new proteins with therapeutic potential. Tsoni[1] states that a salamander's blastema formation is characterized by synthesis of more than 130 unique proteins; during dedifferentiation 26 new proteins are made. These are two hallmarks of salamander regeneration. Globular masses could be another form of regenate proteins. More recent DNA studies show several hundred genes are involved with blastema formation when compared to normal limbs.

Plastic Wrap Effects on Regeneration Rate

Covering scar tissue with plastic definitely accelerates regeneration. It also makes photography more interesting. Two other benefits may come from covering regenerating areas: retaining moisture (similar to a fetal skin regeneration environment)[22] and preventing free iodine evaporation.[21]

Hair Self-Amputation

The finding of purposeful hair movement is startling. The only movement we are aware of is hair erection when a person is emotionally upset.

Self-amputation of hair was another unexpected finding. But hair is strong and could add to tissue strength. We know scars are 70% as strong as intact skin, thus hair imbedded within regenerating tissues would strengthen it.[15, p..35]

How much cell signaling hair does is unclear. Many methods using hairs, from touch to electrical signals, could be passing information to cells and coordination centers.[16]

Antisepsis and Regeneration

In a committee report to decide on the merits of reintroducing iodine for antisepsis, it was emphasized that iodine may be doing more in wound healing than just antisepsis.[17] This agrees with the findings of this case report.

Sponges (Porifera)

Sponge iodotyrosine content reaches 14% of total sponge amino acids, but the percent of iodothyronines (thyroid hormones) have not been reported. Sponges have possibly the greatest ability to regenerate of any animal; small pieces of tissue regenerate whole animals.[18][19]

Flatworms (Platyhelminthes)

Even with complex internal structures, flatworms regenerate when cut in half. Flatworms lack a circulatory system (a network of vessels carrying fluids, oxygen, and food molecules to parts of the body). Consequently, all flatworm cells must be within diffusion distance of oxygen and food. This relationship is possible because flatworms have thin bodies and highly-branched digestive cavities. This structure would encourage access to ocean iodine at all times.[19, p.420, p.428][20, p.499]

Treatment Potential and Verification

If verified, regeneration induced by topical iodine could be a treatment approach with significant potential. But even before that potential is realized, scientists, patients, and physicians should examine regeneration. As results reported here have taken three years and are still incomplete, further results may take some time to examine.

Acknowledgment. I would like to acknowledge the support and advice of Dr. Nasser Shojania, dermatology pathologist.

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Thyroid Science 3(7):CR1-9, 2008 www.ThyroidScience.com *Case Report*

Regeneration of Human Scar Tissue with Topical Iodine: A Preliminary Report—Part 2

David M. Derry, MD, PhD*

*332-425 Simcoe Street, Victoria B.C. Canada, V8V 4T3
Contact: dderry@shaw.ca

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Abstract. This paper adds (to Part 1) details of human scar regeneration with topical iodine and examines hair's role, epithelial layer transparency, and structural units. Topical iodine starts regeneration within a few days. Hair's main new activity is the ability to move freely and on its own to all parts of the regeneration field within its reach. Hairs, within regenerating areas and with help from nerves and arrector pili muscles, are capable of reaching cells accurately anywhere within its reach in any direction. At the same time, follicles appear to make regenate material and transport it along to hair ends by unknown mechanisms which mimic sebum transport from sebaceous glands attached to follicles. Regenate material on hairs is discontinuous; and hair may use touch, electrical signals, regenate material, and coding to signal other cells. Globular regenate material is not discussed here.

Classic studies emphasize the epithelial layer's importance in covering wounds immediately and its important functions in regeneration landmarks. This epithelium is quite transparent in photographs; the transparency affects photographic results. Camera angles perpendicular to skin surfaces allow observation in detail of structures inside the body or below the surface of epithelial layers. This method can be described as an *in vivo* microscopy for watching human tissue activity. Cellular structure is not apparent in most regenerating tissue (which is understandable) as camera magnifications are inadequate to examine cells microscopically. There are much larger structural "units" with unknown function. Hair self-amputation is ubiquitous and may be an important part of tissue strengthening and scaffolding. Physical properties, behavior, and reactions with iodine and tissues allow the suggestion that regenate material may be a mix of sebaceous and mucous secretions similar to saliva. Theoretical aspects of these phenomena and treatment potential await other scientists' results.

Keywords. Epithelial • Hair • Human scar • Regenate material • Regeneration • Transparent

Introduction

Early Changes in Wound Healing and Regeneration

Tsoni[1] and Clarke[2] review limb regeneration and wound healing literature. There are a number of well established observations related to early overgrowth of special epithelium before healing or regeneration can take place. If this epithelial layer is removed, regeneration processes and healing stop.

Importance of Hair

In a previous paper, time-lapse-type photography of regenerating scars suggested that hair is important to regeneration.[3] Hair moves in any direction to any locality within its reach, and transports white material (called regenate material) to different cells in regenerating areas. Hair also self-amputates. At times, together with its follicle, a hair stub disappears only to reappear later and re-grow back to normal lengths.

Potential for Cell Signaling of Different Types by Hair

Cell signaling is being intensely studied, and it is possible that hairs have one or more such systems built into their activities. Touch and electrical stimuli could be significant. Regenate material traveling to hair ends by unknown mechanisms is discontinuous and could be used for signaling.

Epithelial Growth over Wound

Epithelial cells grow rapidly over wounds and provide a continuous cover. This layer is biochemically different from the dermis and has important effects on tissues underneath it. It is innervated early but does not need innervation for regeneration to occur, whereas nerves are essential for remaining tissues to regenerate. Epithelial layers send chemical signals to underlying cells that help blastema cell formation and dedifferentiation—two key events in salamander regeneration.[1]

Epithelial Layer Transparency

Photographs of regenerating tissue indicate that epithelial layers growing over wounds are transparent. No other explanation seems plausible. This is important because epithelial layer transparency alters photographic results.

Methods

Lugol's Solution Applications and Plastic Wrap

Methods used were described previously but quite simple.[3] If topical iodine in the form of Lugol's solution (iodine in water) is applied daily to human scars and then covered with plastic wrap, regeneration begins within two or three days. Regeneration stops gradually over a few days when iodine applications are stopped.

If iodine applications are stopped, a normal adult scar forms that is compatible with the current state of regeneration. At the terminal stages of regeneration, adult scars either do not form or are slower forming. There may be final regeneration stages in which formation of adult scars is not the best alternative.

Regeneration appears to make new tissues compatible with the age of surrounding tissues. That is, if surrounding tissues are wrinkled from age new healed areas will usually have wrinkles. There is no evidence yet of rejuvenation (younger tissue made) from topical iodine. In addition, loose skin anywhere on the body (from losing weight after a period of obesity) is not affected by iodine regeneration. So far, it appears that iodine-induced regeneration requires scar tissue of some form to be initiated.

Cameras: Nikon Cool Pix

Five different Nikon Cool Pix cameras with mega pixels between 5 and 8 were used to record regeneration progress. Each camera had a zoom lens for magnifications of about 7x; one camera had an enlarging attachment which allowed magnifications up to 20 times. This attachment, however, was awkward because of a fixed stand.

Scars

There are four scars. One is a 50-year-old scar on the face from surgical removal of a mole. Another is an abdominal scar 18cm long opened three times before final closing. (All bowel function was normal for the three years of the present study.) A colostomy scar and a 2.5cm scar on the left wrist complete the list.

Controls

Only internal controls were possible in these experiments and consisted of different types of scars of all sizes and degrees of damage and age. In addition, regeneration was started and stopped repeatedly for variable lengths of time, the longest period being four months.

This paper, like Part 1, documents observations to date on regeneration from topical iodine. Over a three-year period much information has been recorded, but the largest scar still will be regenerating for at least another year or two. This large scar is continuing to yield important data on regeneration. The smaller wrist scar is in terminal stages of regeneration and has been purposely slowed and intermittently stopped to extract as much information as possible before regeneration ends. When that happens, no further information will be available.

Results

Hair and Regenate Material

Where possible the author has used wrist regenerating fields for illustration. This includes the two coordinating centers in the photographs both for size comparison (they are 5mm apart) and for reader orientation. Without these stationary markers, it is easy to be visually confused.

There are two types of regenate material, a white snow-like and a globular form. Only the first type will be examined here; the globular form will be discussed later. All references to regenate material in this paper are to the white snow-like type. (See Derry.[3]) Regenate material under plastic wrap is seen at all sites in one or both forms. Photographs suggest that one major source of regenate material is hair follicles. The newly formed regenate material moves up hair ends by unknown mechanisms for distribution to tissues.

Hair and Units

During the recording of hair activities in regeneration fields it was helpful to identify each frequently seen hair by number. Hair follicles and coordinating centers do not change locations. Figure 1 shows wrist regenerating areas immediately adjacent to the two coordinating centers. The centers are 5mm apart and straddle the radial artery, which is not visible in the picture but comes down from the left upper corner to pass between the two centers and then on to the left side of the hand (the picture's right side). Hairs sitting on the radial artery have small oscillating movements noticeable at their ends corresponding to heart beats. There is always a palpable but invisible ridge between coordinating centers throughout regeneration (3 years). As this is a left wrist photograph, fingers (distal) are right and the body (proximal) is left. Hair #1 is identified as originating in a follicle about 2-3mm to the left and 1mm down from the upper center. In Figure 1, hair #1 is on the left side curving downwards and further towards the left. The shortness and the blunt end indicate that it has self-amputated earlier to about one-third of its normal length.

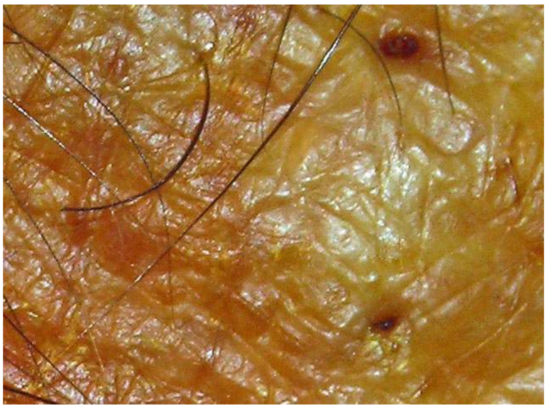

Figure 1. Photograph of the wrist scar area. There are two coordinating centers; both store iodine. A number of hairs all deliver regenerate material to tissues. The tissue non-uniformity displayed is partly related to epithelial layer transparency as well as live tissue complexity. Free iodine in Lugol's solution stains the epithelial layer a brown color seen throughout the picture. Areas where unusual details appear are areas where visualization through transparent epithelial layers is possible. The self-amputated and shortened hair #1 is seen curving to the left on the left side and services a unit on that side. The longer hair coming down from the top is hair #2. Hair #2 tapers to a very thin almost invisible hair towards its end. It has regenerate material on it as do other hairs on the left side. On the upper right, two hairs are servicing "units." As it is 5mm between the two coordinating centers, this unit is about 2mm in diameter. This is 10 times normal cell size. Most details change within minutes to an hour.

The self-amputated hair #1 in Figure 1 is "servicing" (delivering regenate material and/or information to) either a large cell or a larger structure named here as a "unit." Units seem to be a part of regeneration. There are a number of "units" between the two coordinating centers, two of which are being serviced by hairs near the upper coordinating center. At hair #1's follicle there is suggestive evidence of some white regenate material.

Although it is difficult to see where every hair ends, all the ends seem to have specific sites in "units" they reach and touch. It is remarkable how, over a week, a hair will go to many locations of regenerating fields but when it returns to this unit site, for example, it goes to the same place within the unit. This suggests that the mechanisms controlling hair movement, such as nerves and arrector pili muscles, have an ability to place hair ends accurately. Sometimes two or more hair ends will congregate within one unit. Hairs can also disappear under the skin surface and then surface again later at the same site. Regenate material can be seen on hairs.

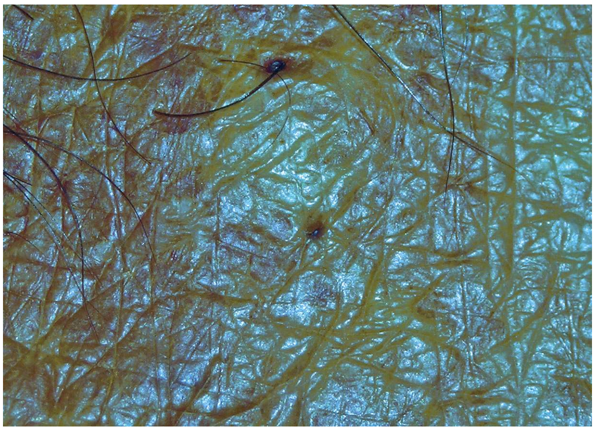

Figure 2. Photograph of the wrist coordinating centers with self-amputated hair #1 "servicing" the upper coordinating center. The small hair to the left of the upper coordinating center may be touching hair #1. During the time the hairs touch, regenate material and possibly signals are exchanged between them.

Hair Self-Amputation

Self-amputation is a constant ubiquitous finding in regeneration. Hairs cut themselves off usually less than half way to the end. This can be followed by regrowth back to normal or self-amputation down further even to follicles leaving only a hair stub. Hairs self-amputated at varying lengths, including one centrally placed stub, are well illustrated in Figure #5.

All hairs with blunt ends in regenerating fields are likely to be previously self-amputated, and the long, tapering, disappearing hairs are intact. The hair self-amputation cycle repeats many times. But the cycle differs from hair to hair and may be geared to tissue needs. Hair #1, the first observed and photographed, self-amputated about a third of the way up the fiber and stayed like that for a week or two. It then self-amputated again to a stub at the follicle. (See Derry.[3]) Other hairs may self-amputate once and then grow back out to normal length. Even the hair stubs function.

Hair #1 is about one-third of its normal length in Figures 1 and 2. Figure 1 shows it servicing a unit on the left. In Figure 2, it services the upper coordinating center. Tissue sites where stubs have disappeared are visited by other hair ends, which appear to service the sites even without the visible presence of any hair or follicle. In spite of disappearing from our view or seeming non-functional, stubs and areas where hair was before disappearing are still part of regeneration.

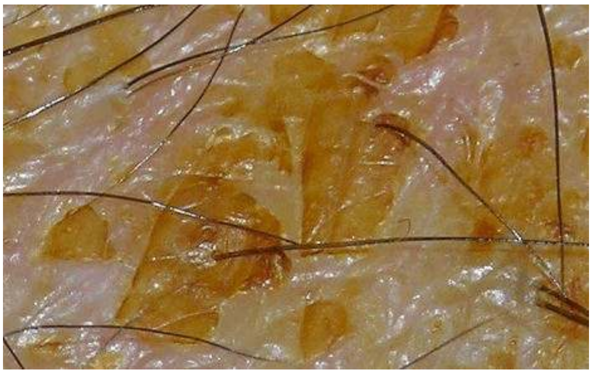

Figure 3. Photograph of the wrist area regeneration demonstrating regenate material gathering at the hair follicle areas prior to transport up the hair. There is regenate material on the hair on the right, and there are many examples of regenate material on other hairs. The brown stain is only in the epithelial layer; there is no visual evidence that tissues stain below epithelial layers. There are two examples of double hair follicles, down in the right corner and up in the left corner. Each hair can go its own way.

Hair #1 and Inter-Hair Touching

In Figure 2, hair #1 is turned around and while "servicing" the upper wrist coordinating center is in contact with a small hair that appears in both Figures 2 and 5. This touching of two hairs may often involve transfer of information or regenate material between the hairs. The transfer of regenate material between hairs is a common occurrence. Throughout much of Figure 2 large structures called "units" are seen whose function is unknown but are found throughout regeneration. None of these units stay looking the same for even a few minutes.

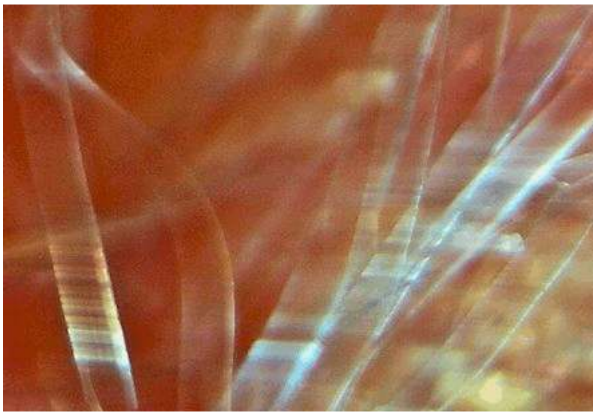

Figure 4. Regenate material moving along hairs is discontinuous. This is seen more clearly when hairs with regenate material on them are moved and photographed at the same time. The patterns are similar to bar codes seen in the grocery stores.

Figure 3, the wrist regenerating field, is a simpler picture in order to show at least one possible source of regenate material. This area is above the two coordinating centers and illustrates a number of points. The brown stain is free iodine within epithelial cells. The pieces of epithelium are alive and functioning since the dose of topical iodine was correct. There does not appear to be any brown stain deeper than the epithelial layer. Hair follicles readily take up iodine stain or are found near pieces of epithelial tissue containing iodine.

The follicle in the lower center of Figure 3 shows regenate material around it. Other hairs show regenate material transporting along hair fibers. In this picture stained epithelial tissue continues as part of regeneration until used up, especially if covered. But as mentioned in the first paper,[3] free iodine evaporation is rapid in the early stages after staining.

Figure 3 contains two examples (right lower corner and left upper corner) of follicles with two hairs coming out of one follicle. As we see from the two hairs in the left upper corner, individual hairs can go to their own destinations. Only occasionally do pairs of hairs travel together to the same site.

The previous paper[3] mentioned the discontinuity of regenate material on hair. In Figure 3 the hair coming from the left center shows discontinuous regenate material. Regenate material on hairs is difficult to photograph (these are at camera magnification limits). Yet seen through the camera screen, discontinuity is quite clear. Regenate material often looks like dots and dashes. But when regenate material on hair is photographed while hair is moving, we get a different picture of regenate material's discontinuity. There is a similarity to the bar coding widely used in society. This more clearly demonstrates discontinuity.

Epithelial Covering, Camera Angle, and Transparency

From many decades of research we know that epithelial cell layers rapidly covering wounds is important for initiating and sustaining regeneration in salamanders. Many photographs of regeneration with unusual visual results suggested the idea that epithelial layers must be transparent. Only transparency would explain the visual findings.

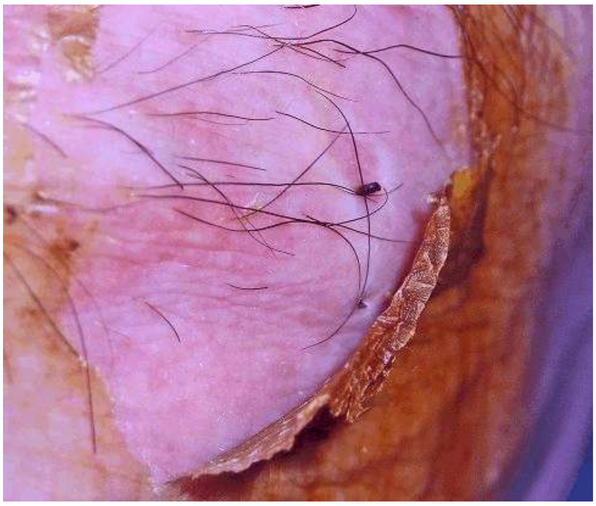

Figure 5. Photograph of wrist regeneration field at an angle from the left to reveal the coordinating centers, the underside and thickness of epithelial layers, and the effects of epithelial layer transparency on the results. The text describes the four epithelial layers that have formed here to protect the regenerating field. Excess iodine was purposely applied to kill, by apoptosis, epithelial layer cells. Also, the wrap was removed to allow tissues to dry. The epithelial layer is thin, perhaps only one or two cells thick. The tissues started to lift and peel as soon as the underlying skin wound was protected by a new epithelial layer. Note on the left where the amount of iodine present at the periphery of the apoptotic stain remains attached to underlying tissue. The amount of iodine at the periphery was at a sub-apoptotic level. During the process, the coordinating centers, although storing iodine, do not seem to be altered.

Epithelial Layer Transparency

Regenerating tissues handle excess iodine by killing surface epithelial cells and reacting with released proteins (apoptosis).[3] With experience, it is possible to add excess iodine to the point that only the epithelial layer dies. This is shown in Figures 5 and 6.

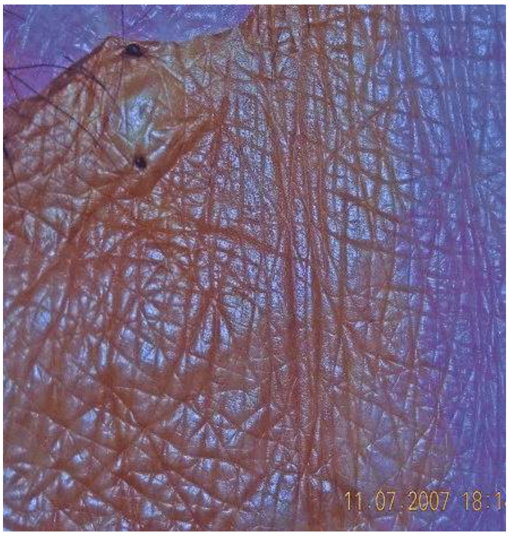

Figure 6. This shows the appearance of the dead peeling epithelium seen in Figure 5 from a perpendicular angle; this photograph was taken before Figure 5. The two coordinating centers are at the top above the peeling epithelial layer. Outlines of underlying tissue are seen. This result suggests a new epithelium formed on the dying and peeling epithelium. See text for explanation. Thus, new epithelial layers form above and below dead epithelium to continuously protect regenerating tissues.

After applying excess Lugol's solution, the author removed the plastic wraps and allowed the tissues to dry. Waiting until the epithelial layer started lifting, the author peeled some of it away to see the wrist coordinating centers. (See Figure 5, the two black dots filled with stored iodine). Figure 6 is a photograph of the same epithelial layer before the layer has lifted enough to clear the coordinating centers. (Figure 6 was taken before Figure 5.) The two dark dots up in the left corner of Figure 6 are stored iodine in the two centers still sitting on top of the peeling epithelial layer.

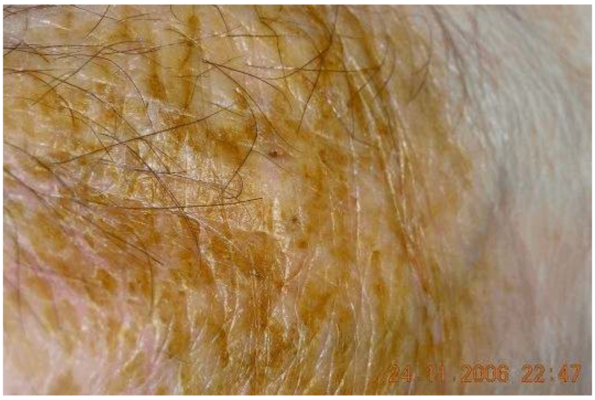
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Figure 7. Angled photograph of wrist regenerating area (similar to angle in Figure 5). The two coordinating centers are in the middle. Most of the whole area appears flat, uninteresting, and divided into large square areas resembling farmers' fields as seen from an airplane. There is no indication of the underlying complex structures and regeneration activity seen in perpendicular photographs. The upper coordinating center is filled with iodine; the lower center is below it. One hair is almost covered in regenate material and shows white in the photograph in the middle center. The area of the right lower quadrant of this photograph (approximately between the date stamp and the lower center) is seen in Figure 8, but with a perpendicular view. The differences are striking.

Four Epithelial Layers in One Picture (Figure 5)

On the basis of the epithelial cell layer's behavior and staining characteristics, together with the assumptions that it is transparent and continuously trying to prevent by all means exposure of the regenerating field, we can suggest where the epithelial layers are in Figure 5. Literature emphasizes that epithelial layers cover wounds within hours and continue covering wounds until healing finishes. If the epithelial layer is removed, regeneration stops. The photograph in Figure 5 was taken at an acute angle from the left in order to see more clearly both coordinating centers and the underside of the peeling epithelial layer. (The camera angle is similar to the one used for Figure 7.) One unusual finding in Figure 5 is that only areas sharply in focus are those with no epithelium on them (the two coordinating centers, the underside of the peeling dead epithelium, and the hairs).

First Epithelial Layer. At the bottom, closest to live tissue, mostly white opaque tissue appears after removing part of the peeling dead epithelium. This skin tissue has been rapidly covered with a new epithelial layer because the original layer has died from excess iodine and is peeling off. Because of the angle no details of tissue structure are evident in the white opaque area to confirm the presence of the transparent epithelial layer.

Second Example of Epithelial Layer. The original epithelial layer on the wound has died by apoptosis after excess iodine application. It appears to be one or two cell layers thick. The excess iodine is being carried away to slough off dead tissue as the plastic wrap is removed.

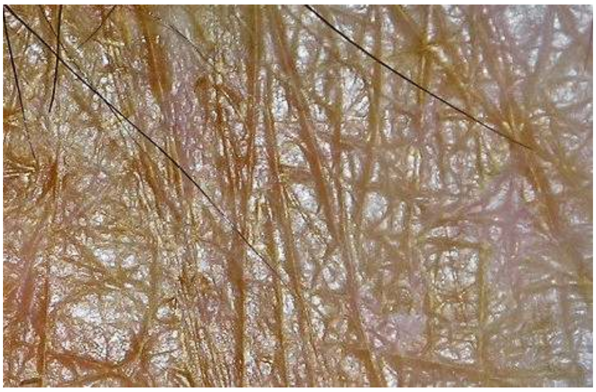

Figure 8. Photograph of activities and structures seen through the epithelial layer in the area above the date stamp in Figure 7. The appearance of the units is constantly changing. The units are generally 10 times bigger than cells and their function is unknown. The long straight brown lines are previously laid down self-amputated hairs forming part of regenerating tissue.

Third Epithelial Layer (on the Left of the Photograph). This layer on the left was part of the original epithelial layer, most of which is now stained brown and peeling in the middle. But because there was less iodine at peripheral parts of the stain, these peripheral epithelial cells did not die. This part of the epithelial layer on the left is lightly stained and still attached to the underlying skin tissue. Even looking at this small piece of the field, there is little to see because of the acute camera angle. As the bigger original layer peels off it rips away from the layer on the left.

Fourth Epithelial Layer. As the original layer started to die, signals to cover the dying regenerating layer again with fresh epithelial cells were sent out. Thus, the brown blurry area on the right side is another epithelial layer overlying the dead layer. In this manner regenerating scars are constantly protected from exposure to the atmosphere by epithelial layer activities.

A perpendicular picture of the peeling epithelial layer in Figure 5 is shown in Figure 6. The two coordinating centers are up in the left corner still on top of the epithelial layer. (The photograph for Figure 6 was taken before that of Figure 5.) We see in Figure 5 the centers both came through the dead peeling layer easily.

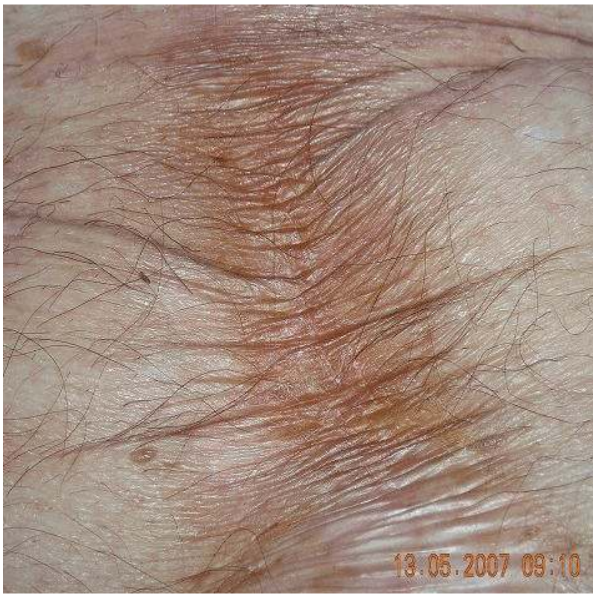

Figure 9. Photograph of the lower half of the large 18cm abdominal scar. The crossing “fingers” of regeneration are seen at intervals down the scar. The picture is taken from above and perpendicular to the scar surface. The area immediately above the date stamp is the umbilicus.

In Figure 6 we start to see some details of the underlying structures but they are not as good as in Figure 8, which is a picture of the same area at another time. The peeling epithelial layer in Figure 6 was dead and had more iodine in it than necessary. Since it was not as transparent as live tissue, we get the inferior image in Figure 6.

In Figure 5 the underside of the peeling epithelial layer shows units more clearly, as we would expect. Thus, with the presence of four epithelial layers the regenerating surface is protected.

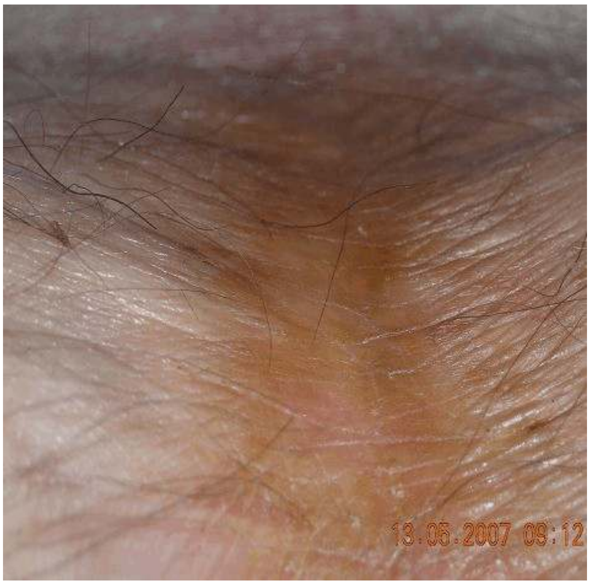

Figure 10. Photograph of same lower half of the abdominal scar taken two minutes after Figure 9 as shown on date and time stamps. This is exactly the same scar and the same area, only the angle of the photograph in this picture is acute rather than perpendicular to the scar. The difference between the two photos is striking. This confirms that there is a transparent layer of epithelial tissue overlying the scar. This layer is essentially invisible to the naked eye but not to the camera.

Macroscopic Views of Regenerating Area to Appreciate Transparency

Figure 7 is a photograph taken from the left at an angle and at low magnification of wrist regenerating areas. Note the two wrist coordinating centers with some iodine in them in the center. Most of the field consists of large square areas (5mm between the two centers) that are reminiscent of farmers’ fields seen from an airplane. Regeneration is proceeding under this layer but we are not aware of it.

Transparency from Perpendicular Angle to Tissue. Figure 8 is a photograph of the same “flat farmers’ fields” area above the date stamp in Figure 7. The picture is taken perpendicular to the area. The amount of detail is not only overwhelming but continues to change within minutes.

Transparency on a Larger Scale. To show again epithelial layer transparency in a different location, Figures 9 and 10 are two photographs of the 18cm abdominal scar below the umbilicus that were taken two minutes apart (as seen on the date-time stamps). Figure 9 is photographed perpendicular to the bottom of the scar. The presence of "finger-like" projections on both sides (mentioned previously[3]) is easily seen. The size of the crossing fingers varies. The large ripples in the tissue in and around the date-time stamp are from regeneration over the umbilical area. Half-way up the picture on the left side, there is a small black object which may be small globular regenate material.

Same Photograph Two Minutes Later at an Angle. The photograph in Figure 10 is zoomed in further to eliminate umbilical focusing interference. But more importantly, it was taken two minutes after Figure 9. On closer view, the small dark object on the left may indeed be small globular regenate material. But shock comes from scar area appearance being so different. It is now covered in smooth, slightly stained material. This is the transparent epithelial layer covering the lower scar area.

Discussion

Hair

Hair may have multiple roles to play in regeneration. If this proves to be so, then it will bring to the attention of researchers something we have largely ignored. Perhaps hair has even more functions than are sketched here. Iodine stimulates all regeneration hair growth. Clinically, hair loss in women can be restored with adequate iodine supplementation.

Cell Signaling

It is reasonable to think that hairs with the type of controlled mobility observed in this case report would have cell signaling capabilities. Touch and electrical signals seem to be probable. Signaling via regenate material is more complex but possible. First, the regenate material by itself could signal. Only regenate material's discontinuous appearance makes possible— as in Figure 4—a suggestion of bar coding. All of this is speculative, but in light of the results these are reasonable questions to ask.

Epithelial Transparency

The literature emphasizes that the epithelial layers growing immediately over a new wound are biochemically different from normal dermis, and that they play major roles in regeneration outcome. This type of epithelial layer also synthesizes proteins which are specific to the layer. Removal of this layer stops regeneration. The layer can phagocytose wound debris, and by histolysis of underlying cells aid dedifferentiation of cells (in salamanders).

The first detectable change starting regeneration is covering of the wound with this special epithelium. The epithelial cells rapidly migrate inwards to cover wounds without mitosis or DNA synthesis.[1] Once cells meet in the middle they become innervated, but epithelial innervation is not essential for regeneration. It is thought that this epithelium sends important signals to underlying tissues to start regeneration. The main point regarding transparency is that it alters our view of tissues.

The photograph in Figure 4 is blurry where there are epithelial layers. Whereas hair, coordinating centers, and the underside of the peeling epithelial layer are the only places where there are no epithelial layers—thus, they are all in sharp focus. When the camera is shot at an angle, the site of probable epithelial layers is demonstrated by blurriness and opaqueness.

Units and Cells

Although tissue subdivisions which are considerably larger than cells have been referred to as "units," there is no real understanding of what they are or how they function. They are mostly formed from even larger nondescript structures and subdivided by hairs as they fall across the units (this is followed by hair self-amputation). If these structures function as one unit, then there is no consistent evidence of intracellular organelles. Normal body cells are around 0.2mm, while the units seen here are often 10 times that size.

Human skin becomes rougher and bumpy with age, and cameras at maximum magnification (3-20 times) have narrow depths of field.[7] This leads to sections being out of focus, and in many photographs this is true. But repeated photographs of the same skin in a live person show different results. The reason for this difference, from the photographs presented here, appears to be epithelial layer transparency. When looking directly at skin, we in fact are looking below the surface of the epithelial layer—something artists have appreciated for centuries. Skin tissue observed with cameras during regeneration can be classified as a form of *in vivo* microscopy; almost everything in these pictures is alive.

Possible Chemical Nature of Regenate Material

Since regenate material sources seem to be hair follicles, there are two relevant excretions from the skin. Sebum from sebaceous glands attached to hair follicles contains exclusively lipid products such as cholesterol, squalene, fatty acids, and waxes. Sebum is secreted by a type of cell disintegration called holocrine secretion. Normally, sebum secreted onto hair is transported up the hair the same way regenate material is transported during regeneration.

During regeneration of scars under plastic wrap, moisture accumulates with white regenate material. This moisture could be water soluble mucins. The available moisture would increase mucin secretion by surface epithelial mucous cells. The parotid and submaxillary glands have both sebaceous and mucous cell secretions. Oral cavities have numerous separate sebaceous glands.[4] Saliva, as a final mix, has both water and lipid solubility properties.[6]

Mucins are huge water soluble complex proteins containing thousands of amino acids. These molecules, with molecular weights sometimes in the millions, have highly glycosylated protein cores with multiple oligosaccharides and complex tertiary structures. The sebum, on the other hand, is a lipid mixture. In addition, epidermal cells undergo sebaceous transformation under stress.[4] The regenate material on skin scar regeneration fields is likely a mix from these two sources.[4][5][6][8]

Conclusion

One cannot help but be impressed with regeneration's almost unlimited flexibility. Even fetal development does not have this property. If completely regenerated scars are opened again, it seems certain that iodine applications would start the regeneration process once more. There appear to be no age limits to regeneration's effectiveness. If a new wound occurs in regenerating scars, again the process adapts and begins healing both scars in a coordinated fashion. Only the arrival of finished normal tissue stops regeneration (from what has been observed so far). Regeneration is one of Nature's most complex, mysterious, and magnificent accomplishments. Unraveling how and why it works will take many years. In the meantime, because treatment procedures using this approach are harmless, if care is taken, physicians and patients can use this treatment to their benefit while scientists work to solve regeneration's mysteries.

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Autoimmune Thyroiditis: Correlation of Cytomorphology with Drug History and Clinical Implications

(**Full Text Free** in pdf format)

Somanath Padhi, MD,[1] Renu G'Boy Varghese, MD, DNB[1]*
Anita Ramdas,1 MD, Kulwant Singh, MD,[1]
Jayaprakash Sahoo, MD, DM,[2]
Mark C Arokiaraj, MD, DM,[3]

Department of [1]Pathology, [2]Endocrinology, and [3]Cardiology,
Pondicherry Institute of Medical Sciences,
Ganapathychettykulam, Kalapet, Puducherry, India, 605014

Correspondencing Author: Dr Somanath Padhi, MD
Assistant Professor, Department of Pathology
Pondicherry Institute of Medical Sciences
Kalapet, Puducherry, India, 605014
Phone: 91 0413 2656271 Fax: 91 0413 2656273
Email: somanath.padhi@gmail.com

Abstract. **Background**: The cytopathologist plays an important role in the evaluation of thyroid cytomorphology in various neoplastic and non-neoplastic conditions. However, thyroid cytomorphology and the clinical implications of drug usage have rarely been discussed. Nonetheless, drugs used for different non-thyroid conditions may influence the hypothalamic-pituitary-thyroid axis and cause diverse cytomorphological patterns on aspiration smears. Clinicians should be informed of the presence or absence of specific underlying thyroid abnormalities detected on cytosmears which may warrant complete drug withdrawal, dose reduction, or change to different drug combinations. Besides these outcomes, interpreting thyroid cytomorphology, without a prior knowledge of antithyroid drug therapy, can be challenging and lead to misdiagnoses of neoplasm or malignancy. **Cases**: We present the thyroid cytomorphology of 3 different patients, each of whom was receiving a different drug (amiodarone, carbimazole, and carbamazepine) with biochemical, serological, and ultrasound correlations. We also briefly review the relevant literature. We conclude that a proper drug history is important while interpreting thyroid cytology in different clinical settings.

Keywords • Amiodarone • Carbimazole • Carbamazepine • Cytomorphology • Drugs • Thyroid

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Case Reports

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Somanath Padhi, MD,[1]* Renu G'Boy Varghese, MD, DNB[1]
Anita Ramdas,[1] MD, Kulwant Singh, MD,[1]
Jayaprakash Sahoo, MD, DM,[2]
Mark C Arokiaraj, MD, DM,[3]

Department of [1]Pathology, [2]Endocrinology, and [3]Cardiology,
Pondicherry Institute of Medical Sciences,
Ganapathychettykulam, Kalapet, Puducherry, India, 605014

**Corresponding Author*: Dr Somanath Padhi, MD
Assistant Professor, Department of Pathology
Pondicherry Institute of Medical Sciences
Kalapet, Puducherry, India, 605014
Phone: 91 0413 2656271 Fax: 91 0413 2656273
Email: somanath.padhi@gmail.com

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***Abstract*. Background**: The cytopathologist plays an important role in the evaluation of thyroid cytomorphology in various neoplastic and non-neoplastic conditions. However, thyroid cytomorphology and the clinical implications of drug usage have rarely been discussed. Nonetheless, drugs used for different non-thyroid conditions may influence the hypothalamic-pituitary-thyroid axis and cause diverse cytomorphological patterns on aspiration smears. Clinicians should be informed of the presence or absence of specific underlying thyroid abnormalities detected on cytosmears which may warrant complete drug withdrawal, dose reduction, or change to different drug combinations. Besides these outcomes, interpreting thyroid cytomorphology, without a prior knowledge of antithyroid drug therapy, can be challenging and lead to misdiagnoses of neoplasm or malignancy. **Cases**: We present the thyroid cytomorphology of 3 different patients, each of whom was receiving a different drug (amiodarone, carbimazole, and carbamazepine) with biochemical, serological, and ultrasound correlations. We also briefly review the relevant literature. We conclude that a proper drug history is important while interpreting thyroid cytology in different clinical settings.

Keywords ● Amiodarone ● Carbimazole ● Carbamazepine ● Cytomorphology ● Drugs ● Thyroid

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Introduction

Thyroid autoimmunity encompasses two extremes: at one end, the diffuse hyperplasia and hyperfunctioning gland of Graves' disease; and at the other, total destruction of the gland with hypothyroidism (as in Hashimoto's thyroiditis).

Hashimoto thyroiditis is the most common cause of hypothyroidism in iodine sufficient areas of the world.[1] Fine needle aspiration cytology of thyroid is a safe and accurate procedure for the initial evaluation of thyroiditis. This is especially true when correlated with serology, hormone profile, colour Doppler ultrasonography, and radionuclide parameters.[2-6]

However, drug induced cytological changes in thyroid fine needle aspiration, their diagnostic pitfalls, and clinical implications are rarely described in the literature.

Amiodarone, a class III antiarrythmic drug, produces thyroid dysfunction (both hyper and hypothyroidism) in its users with or without underlying thyroid abnormalities. Amiodorone-induced hypothyroidism is amenable to thyroid replacement therapy whereas amiodarone-induced thyrotoxicosis (type 1 & 2) leads to a difficult therapeutic approach. Proper evaluation of thyroid function is, therefore, important both prior to the start and during amiodarone use in cardiology practice.[7-10] Even more problematic is the scenario of unnecessary overdiagnosis of a neoplasm or malignancy in fine needle aspiration smears in patients of untreated Graves' disease or those receiving radioiodine ablation or antithyroid drugs (carbimazole, a pro-drug converted after absorption to the active form, methimazole.).[11-15]

An association of autoimmune thyroiditis during the course of or following antiepileptic therapy is rare, and that after carbamazepine therapy has not been reported in English literature. However, there

Table 1. Clinical characteristics, prescribed drugs, cytological diagnosis of goitre and impact on further management in three different patients.

Age/sex	Department Primary Diagnosis Drug therapy	Secondary presentation (duration)	Cytological diagnosis	New therapy	Remark
48/M	Cardiology CRHD, MR, AF x 6 months tab amiodarone 200 mg x 6 months	Diffuse goitre x 1month Palpitation, hand tremor, weight loss x 15 days	Diffuse toxic goitre	C+P+D stoppage of amiodarone	Withdrawal of amiodarone due to risk of development of type 1 AIT[7,8]
40/M	Endocrinology Graves' disease x 1 year Tab carbimazole 20 mg x 1 year	Reduction in size of goitre, weight loss, heat intolerance present	Toxic goitre, Autoimmune thyroiditis	Tab carbimazole 20mg contd.	TIC, suspicion of neoplasm, diagnostic pitfall.[12,15]
26/F	Neurology Seizure disorder x 9 years Tab carbamazepine (Cz) 200 mg TDS x 9 years	Diffuse Goitre (L > R) x 2years Cold intolerance, menorrhagia, hoarseness of voice, weight gain x 2 months	Hashimoto thyroiditis	Cz+T	Possible association of autoimmunity[16] (significance ?)

Abbreviations: M; males, F; female, CRHD; chronic rheumatic heart disease, MR; Mitral regurgitation, AF; atrial fibrillation, TDS; three times daily, mg; milligram, L; left, R; right, C; Carbimazole, P; Propranolol, D; Digoxin, Cz; Carbamazepine, T; L-Thyroxine (50 microgram), AIT; Amiodarone induced thyrotoxicosis, TIC; therapy induced changes in cytosmear.

are reports to suggest that anticonvulsants may induce or exacerbate autoimmune mechanisms in certain thyroid diseases, the exact pathogenesis of which still not known.[16]

The aim of the present article is to highlight various issues related to drug therapy and thyroid cytomorphology. By doing so, we hope to create awareness among cytopathologists and guide clinicians to more effective patient management.

Case Histories

The 3 cases described in this report involved clinical presentation and fine needle aspiration cytology of the thyroid glands from three different patients (2 male, 1 female). Each patient received a different category of drug (1 antiarrythmic, 1 antithyroid, and 1 antiepileptic). The cytologies are presented in Table 1 and 2, respectively.

Discussion

Amiodarone, a class III antiarrythmic drug, has a strong structural resemblance to the thyroid hormones. It contains two iodine atoms, which constitute 37.5% of its mass. Daily intake of 200 mg of amiodarone increases the iodine level in the circulation 20-to-40 times compared to the general population. The excessive load of iodine causes alteration in thyroid hormone metabolism. Thyroid dysfunction, both hypothyroidism and hyperthyroidism occurs in up to 25% of users. Amiodarone-induced hypothyroidism occurs more commonly in females in iodine sufficient areas. Their hypothyroidism results from the Wolf-Chaikoff effect with blockage of hormone secretion or as a consequence of chronic autoimmune thyroiditis due to iodine excess. The patient with amiodorone-induced hypothyroidism should undergo thyroid hormone replacement therapy. Amiodarone withdrawal is not always necessary.[7,8]

Amiodarone may induce autoimmune thyrotoxicosis more commonly in males in iodine deficient areas 4 months to 3 years after initiating therapy. Type 1 amiodarone-induced thyrotoxicosis is defined as hyperthyroidism occurring in patients with underlying thyroid disease, with or without positive thyroid hormone (Jod-Basedow effect). Patients do not have peroxidase antibody titre. The hyperthyroidism is due to increase synthesis and release of thyroid hormone.

Type 2 amiodarone-ind uced thyrotoxicosis is a drug-induced destructive thyroiditis that occurs in patients without underlying thyroid disorder. Antithyroid drugs such as propylthiouracil/methimazole with withdrawal of amiodarone are the treatment of choice in type I and type 2 amiodarone-induced thyrotoxicosis. Patients respond rapidly to glucocorticoid therapy.[7-10]

In view of potential interaction of amiodarone with the thyroid gland and consequent therapeutic implications, interpretation of thyroid cytomorphol-

Table 2. Cytomorphology of thyroid, hormone profile, serology, ultrasound finding in three different patients on medications for different conditions.

Cases/drug	Cytomorphology	Serology	Thyroid hormone	CD-USG thyroid	Diagnosis
1 Amiodarone (antiarrythmic)	Cellular, pseudopapillae, fire flare, dense cytoplasm, paravacuolar granules, thin colloid, no inflammation.	Anti TPO + ve	Hyperthyroid (undetectable serum TSH)	B/L enlarged gland, heterogonous echotexture, Increased colour flow	Diffuse Toxic Goitre Suggestive of GD[6] (Figure-1A,B)
2 Carbimazole (antithyroid)	Cellular, monolayer sheet, microfollicles pseudopapillae, plenty of bare nuclei, sudden bizarre pleomorphic nuclei, coarse chromatin, occasional paravacuolar granules, mild Hurthle cell change, minimal lymphocytes, absent colloid.	Anti TPO + ve	Euthyroid	Not available at the time of FNAC	Therapy induced changes, suspicious of neoplasm.[11-15] (Figure 2)
3 Carbamazepine (antiepileptic)	Moderate cellularity, Prominent Hürthle cell change, folliculolysis, giant cells, epitheloid cells, prominent lymphocytic infiltration, crushed tissue fragment,[4] scant thick colloid.	Anti TPO + ve	Hypothyroid (elevated TSH)	B/L asymmetrically enlarged gland, nodular outline, heterogenous echotexture, no calcification. Decreased blood flow	Hashimoto thyroiditis.[2-4] (Figure-3A,B,C)

Abbreviations: TPO; thyroid peroxidase antibody, TSH; thyroid stimulating hormone, CD-USG; Colour Doppler ultrasonography, B/L; bilateral, FNAC; fine needle aspiration cytology, GD; Graves' disease.

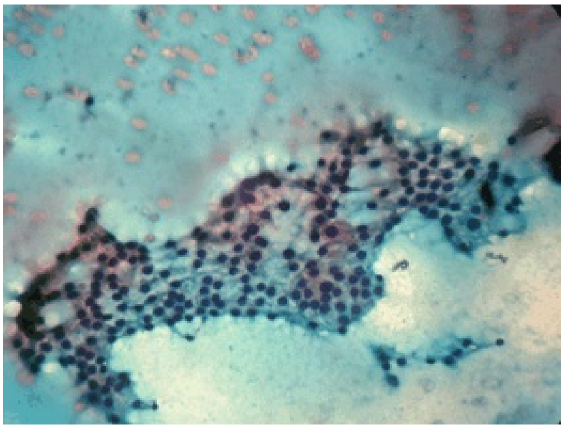

Figure 1A. Cytosmears from thyroid in Case 1 showing sheets of follicular epithelial cells with marginal vacuoles (fire flare appearance) over a background of thin colloid (Papanicolaou stain, 400X). These features are that of a hyperfunctioning state and with a positive serology suggestive of Graves' disease

ogy is important. Cytological features such as fire-flare appearance of the thyrocytes, dense cytoplasm, paravacuolar granules with thin colloid are suggestive of a hyperfunctioning state, whereas Hürthle cell morphology, folliculolysis, lymphocytic infiltration, epitheloid cells, plasma cells, and scant to absent colloid are strongly suggestive of Hashimoto's hyperthyroiditis.[2-6] The presence of positive serology, undetectable serum TSH, and cytomorphology was suggestive of hyperthyroidism in Case 1. Complete withdrawal of the drug was necessary to prevent possible development of type 1 autoimmune thyrotoxicosis.

Worrisome cellularity and nuclear atypia in Graves' disease, with or without prior therapy, can be a potential a source of misdiagnosis of neoplasm. Irradiated follicular epithelial cells, following radioiodine therapy, may show focal regenerative cellular and nuclear atypia, oxyphil or squamous metaplasia or cytoplasmic vacuolization. Bizarre cells with markedly enlarged and cells with nuclear pseudo inclusions may lead to a false positive diagnosis of malignancy. Similar morphology has been described in patients with untreated Graves' disease or those receiving carbimazole therapy.[11-15]

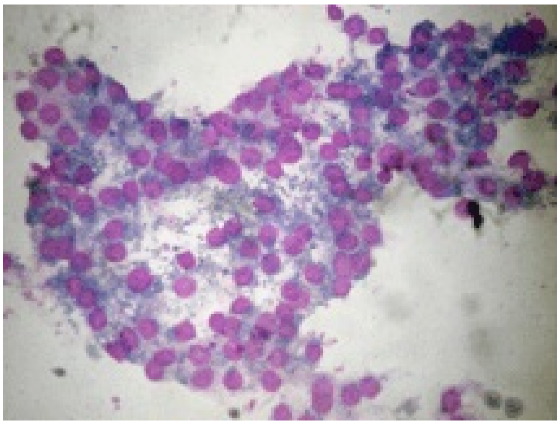

Figure 1B. Bluish green paravacuolar cytoplasmic granules in thyroid follicular epithelial cells indicative of hyperfunctioning state. No evidence of thyroiditis was seen (Leishmann stain, 400X).

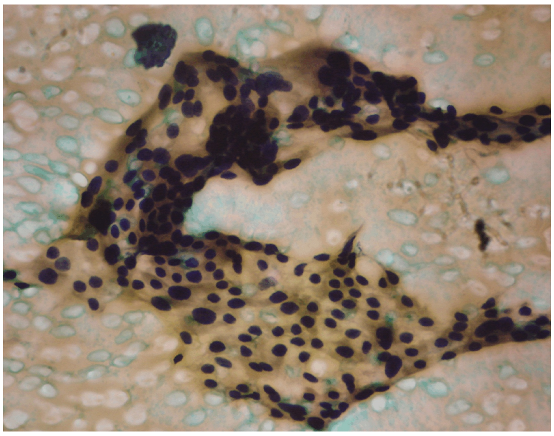

Figure 2. Changes suspicious of neoplasm induced by therapy.

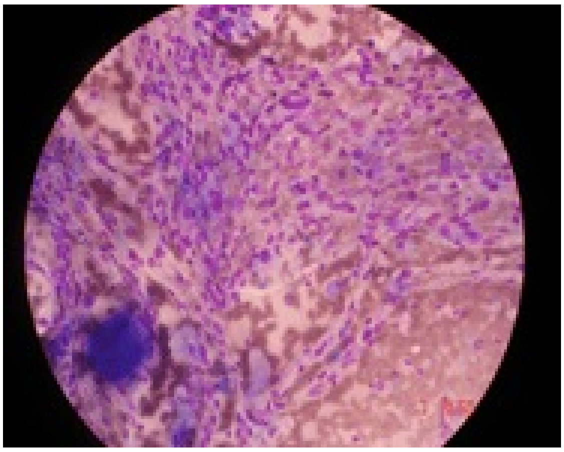

Figure 3C

Figures 3A, 3B, and 3C. Moderately cellular cytosmears from thyroid in Case-3 showing (A) intense lymphocytic infiltration into the epithelial cells, (B) Hürthle cell change), and (C) crushed cellular fragments with epitheloid cells over a hemorrhagic background devoid of colloid. These cytological features are diagnostic of autoimmune thyroiditis (Hashimoto thyroiditis) (Leishmann, 200X, 400X).

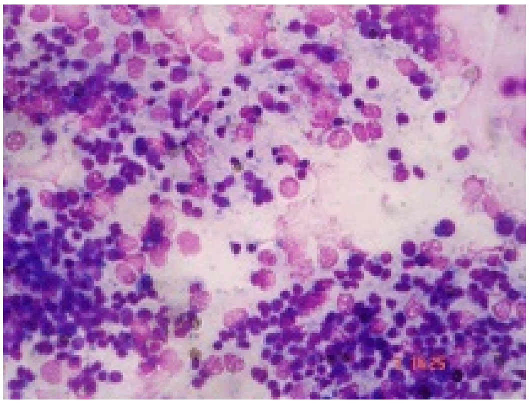

Figure 3A

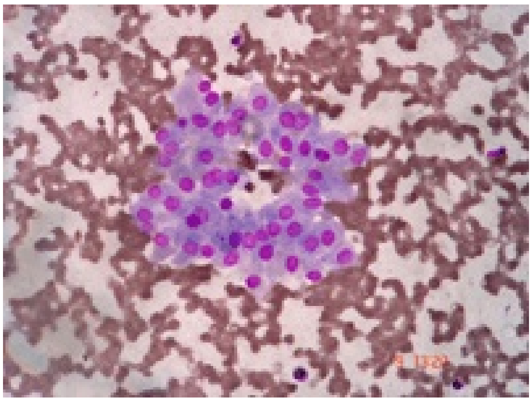

Figure 3B

Demonstrating nucleolar features with toludine blue stain can be helpful in these cases.[12] Obtaining a drug possible development of type 1 amiodarone-induced history with serological, hormonal, and radiological correlation can avoid unnecessary misdiagnosis as in Case 2.

Association of autoimmune thyroiditis with the use of antiepileptic drugs has been rarely documented in the research literature.[16,17]Goitrous hypothyroidism with increased anti-thyroglobulin antibodies and anti-microsomal antibodies has been reported in two adolescent girls 1-to-3 years following antiepileptic (ethosuximide) therapy. Replacement of ethosuximide with valproate in one, and discontinuation of therapy with thyroxine replacement in the other, led to reduced antibody titres with restoration of euthyroid status.[16]

In a recent study by Allison Gandey et al.,[17] it was found that 32% of patients with epilepsy taking antiepileptic drugs in mono or polytherapy have thyroid hormone abnormalities. From a study of 300 epileptic patients, "the most relevant," report, "was the increase of thyroid stimulating hormone (TSH) in patients taking valproate monotherapy (61.5%; TSH level > 6.6; $p < 0.001$)." It is an increase, they caution, that can lead to subclinical hypothyroidism. Forty-eight percent of carbamazepine users and 17% phenytoin users had thyroid abnormalities. Carbamazepine in polytherapy significantly decreased thyroxine levels below 62.01 ($p = 0.008$). These observations suggest that anticonvulsants may induce or exacerbate autoimmune mechanisms in certain thyroid diseases. Autoimmune thyroiditis following the use of carbamazepine in a young female (case 3) in the present series may just be an association, the clinical significance of which is yet to be ascertained. Hence, more cases with similar findings must be studied in order to reach a rational conclusion.

Conclusion

To conclude, interpretation of thyroid cytomorphology can be challenging in various clinical settings. Obtaining a proper drug history is essential while interpreting cytosmears in order to guide the clinicians for better therapy options.

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Thyroid Science 4(6):CR1-8, 2009

Clinical Case Report: Ultrastructural Evidence of Skeletal Muscle Mitochondrial Dysfunction in Patients With Subclinical Hypothyroidism

(Full Text Free in pdf format)

Michael E. Dunn,[1] James V. Hennessey,[2] Arthur C. Cosmas,[1]
Linda S. Lamont,[1] and Thomas G. Manfredi[1]

[1]Department of Kinesiology, University of Rhode Island, Kingston, Rhode Island 02881;
[2]Division of Endocrinology, Rhode Island Hospital, Brown University School of Medicine,
Providence, Rhode Island 02912

Corresponding Author: Thomas Manfredi, PhD, Department of Kinesiology,
University of Rhode Island, Independence Square II, Kingston, RI 02881
Tel: 401-874-5439 manfredi@uri.edu

ABSTRACT. ***Objective:*** The lack of overt signs and symptoms and controversies surrounding the thyroid stimulating hormone (TSH) reference range variability make the management of subclinical hypothyroidism (sHT) a challenge. Because muscle cramps and weakness have been noted in sHT, histological skeletal muscle examination may be of diagnostic significance as the presence of abnormalities would substantiate a significant consequence of the mild thyroid failure presumed to be present in the individual with sHT. The objective of this study was to investigate the ultrastructural and histological changes of skeletal muscle associated with sHT. ***Design:*** Skeletal muscle biopsies from the vastus lateralis were obtained from four subjects with sHT. Samples were fixed, sectioned, and stained for quantitative and qualitative electron and light microscopic analysis. ***Main Outcome:*** Analyses revealed characterizable morphological and ultrastructural alterations and quantitative mitochondrial variations between subjects, indicative of skeletal muscle mitochondrial dysfunction in sHT patients. For the 4 subjects, mean mitochondrial perimeter (MP) was 1.09 ± 0.312 μ, mean mitochondrial area (MA) was 0.10 ± 0.05 μ^2, and mean mitochondrial volume density was 1.92 ± 0.95. ***Conclusions:*** The observed and quantified mitochondrial alterations and the noted morphological and ultrastructural alterations identify previously undocumented pathological skeletal muscle alterations associated with sHT. The observed morphological and ultrastructural alterations lend support to a trend of progression of sHT into overt hypothyroidism as a result of mitochondrial dysfunction and associated metabolic shift. The identification of these skeletal muscle alterations as sequelae of sHT may lend convincing objective evidence of a pathophysiologically significant abnormality in patients with sHT. If so, this should diminish the substantial resistance to treatment of these patients at an early stage of disease and attenuate the progression to overt hypothyroidism.

Keywords: Subclinical hypothyroidism • Mitochondria • Morphology • Skeletal muscle • Ultrastructure

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Thyroid Science 4(6):CLS1-8, 2009 www.ThyroidScience.com *Case Reports*

Clinical Case Report: Ultrastructural Evidence of Skeletal Muscle Mitochondrial Dysfunction in Patients With Subclinical Hypothyroidism

Michael E. Dunn,[1] James V. Hennessey,[2] Arthur C. Cosmas,[1]
Linda S. Lamont,[1] and Thomas G. Manfredi[1]

[1]Department of Kinesiology, University of Rhode Island, Kingston, Rhode Island 02881;
[2]Division of Endocrinology, Rhode Island Hospital, Brown University School of Medicine,
Providence, Rhode Island 02912.

Corresponding Author: Thomas Manfredi, PhD, Department of Kinesiology, University of Rhode Island,
Independence Square II, Kingston, RI 02881 Tel: 401-874-5439 manfredi@uri.edu

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Abstract. ***Objective:*** The lack of overt signs and symptoms and controversies surrounding the thyroid stimulating hormone (TSH) reference range variability make the management of subclinical hypothyroidism (sHT) a challenge. Because muscle cramps and weakness have been noted in sHT, histological skeletal muscle examination may be of diagnostic significance as the presence of abnormalities would substantiate a significant consequence of the mild thyroid failure presumed to be present in the individual with sHT. The objective of this study was to investigate the ultrastructural and histological changes of skeletal muscle associated with sHT.

Design: Skeletal muscle biopsies from the vastus lateralis were obtained from four subjects with sHT. Samples were fixed, sectioned, and stained for quantitative and qualitative electron and light microscopic analysis.

Main Outcome: Analyses revealed characterizable morphological and ultrastructural alterations and quantitative mitochondrial variations between subjects, indicative of skeletal muscle mitochondrial dysfunction in sHT patients. For the 4 subjects, mean mitochondrial perimeter (MP) was 1.09 ± 0.312 ì , mean mitochondrial area (MA) was 0.10 ± 0.05 ì ², and mean mitochondrial volume density was 1.92 ± 0.95.

Conclusions: The observed and quantified mitochondrial alterations and the noted morphological and ultrastructural alterations identify previously undocumented pathological skeletal muscle alterations associated with sHT. The observed morphological and ultrastructural alterations lend support to a trend of progression of sHT into overt hypothyroidism as a result of mitochondrial dysfunction and associated metabolic shift. The identification of these skeletal muscle alterations as sequelae of sHT may lend convincing objective evidence of a pathophysiologically significant abnormality in patients with sHT. If so, this should diminish the substantial resistance to treatment of these patients at an early stage of disease and attenuate the progression to overt hypothyroidism.

Keywords. Subclinical hypothyroidism • Mitochondria • Morphology • Skeletal muscle • Ultrastructure

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Introduction

Thyroid dysfunction affects more than 21 million Americans.[1] Untreated thyroid dysfunction has negative health consequences, including coronary heart disease, osteoporosis, atrial fibrillation, cognitive impairment, and depression. When analyzed as a whole, these negative health consequences resulting directly from untreated thyroid dysfunction are among the nation's largest causes of morbidity, mortality, and diminished quality of daily life in older adults.[1] The incidence of diagnosed hypothyroidism ranges from 4% to 8.5%.[2] Subclinical hypothyroidism is more common in women over the age of 60, (20%)[2] and males ≥ 65 years.[2,3]

Subclinical hypothyroidism represents the earliest stage of thyroid hypofunction.[4] It is diagnosed by an elevation of serum thyroid-stimulating horference range serum free T_4 (FT_4) level of 0.8-2.3 ng/dL.[4] The rate of progression from subclinical hypothyroidism to overt hypothyroidism directly correlates with the patient's initial TSH value,[2] and most experts recommend treatment of subclinical hypothyroidism when TSH values exceed 10 mIU/L. However, 75% of those diagnosed with subclinical hypothyroidism have TSH values in the 5-10 mIU/L range,[5] thereby creating an imprecise barometer regarding the need to and recommendations for the initiation of thyroid hormone treatment.

Typical signs and symptoms of overt hypothyroidism include cold intolerance, dry skin, constipation, depression, myalgia, arthralgia, cramps, and weakness as well as altered metabolic parameters including increased total and LDL cholesterol.[1] Adding to the difficulty in diagnosis, subclinical hypothyroid patients may not present with consistent symptoms. Since myalgia, muscle cramps, and weakness have been reported in subclinical hypothyroidism,[6] a histological examination of skeletal muscle in patients with subclinical hypothyroidism would be important in confirming a physical consequence of subclinical hypothyroidism. However, no literature exists describing the ultrastructural morphological characteristics of skeletal muscle in subclinical hypothyroidism patients.

The purpose of this study was to examine biopsied skeletal muscle of 4 clinically diagnosed subclinical hypothyroid patients and identify ultrastructural and morphological characteristics, specifically mitochondrial alterations, found in the subclinical hypothyroid patients.

Materials and Methods

Subjects. Four patients served as study subjects. Each patient's informed consent for these procedures was obtained as part of the Institutional Review Board (Lifespan Academic Medical Center) approval process. A comprehensive physical examination and medical history review were included in the patients screening. Patients were included if they were ages 21-80 years, had no prior history of hormone supplements in the preceding six months, and had elevated TSH levels with FT_4 levels within reference range.

Patient 1. A 34 year old female weighing 76.7 kg (169.1 lbs) with no family history of thyroid dysfunction presented with a TSH level of 14.33 m IU/L and a FT_4 level of 0.84 ng/dL (Table 1). The patient presented with a weight gain ≥ 6.8 kg (14.99 lbs) over the course of the previous year, cold intolerance and low energy levels characterized by muscle weakness, myalgia, and muscle spasms exacerbated by cold exposure and alopecia. Her sleep pattern and bowel function were normal. At the time of her presentation, she was treated only with an oral contraceptive.

Table 1. TSH, FT_4 Levels and Clinical Symptoms of 4 Patients with Subclinical Hypothyroidism.

Patient	TSH (mIU/L)	FT_4 (ng/dL)	Clinical Symptoms*
1	14.3	0.84	E, W, MW, P, MP, MS, CI, H
2	15.2	0.86	
3	5.5	1.03	E, P
4	11	0.8	E, S, W, MW, P, MP. MS, H

*Decreased energy level (**E**), abnormal sleep pattern (**S**), increased weight (**W**), muscle weakness (**MW**), decreased physical performance (**P**), muscle pain (**MP**), muscle spasm (**MS**), cold intolerance (**CI**), and hair loss (**H**).

Patient 2. A 46 year old male weighing 78.0 kg (172.0 lbs) with no family history of thyroid dysfunction, presented with a TSH level of 15.2 mIU/L and a FT_4 level of 0.86 ng/dL (Table 1). He was not on medication at the time of evaluation. Review of systems revealed no decrease in energy level as measured by physical performance, normal sleeping patterns, no weight change within the last year, no reported muscle weakness, spasm or myalgia and no perceptible intolerance to cold. Bowel movements were normal and there was no evidence of alopecia.

Patient 3. A 49 year old male weighing 83.5 kg (184.1 lbs) with a positive family history of thyroid dysfunction presented with a TSH of 5.5 m IU/L and FT_4 level of 1.03 ng/dL (Table 1). His medications at presentation included Lovastatin, niacin, Metoprolol, Clopidogrel, ASA, and Ramipril. He reported a severe lack of energy characterized by a decrease in physical performance. He reported no weight gain, no muscle weakness, spasm or pain, and no perceptible increase in cold intolerance. His bowel function was normal and no alopecia was noted.

Patient 4. A 44 year old male weighing 70.8 kg (156.1 lbs) with a history of Graves' Disease. He was not on medication and presented with a TSH level of 11.01 m IU/L and a FT_4 level of 0.80 ng/dL (Table 1). He reported a loss of energy, a significant weight

Table 2. Mitochondrial morphometric data of 4 subclinical hypothyroidism patients.

Patient	Mitochondria perimeter (MP) size range (ì)	Mean MP (ì) ± SD	Mitochondrial area (MA) (ì ^{2})	Mitochondrial volume density (MVD)(%)
1	0.40-0.97	0.65 ± 0.14	0.03	1.95
2	0.56-2.25	1.25 ± 0.44	0.12	0.57
3	0.57-3.34	1.11 ± 0.36	0.10	2.55
4	0.53-4.57	1.36 ± 0.52	0.15	2.6

*Mean Patient MP = 1.09 ± 0.312µ; Mean Patient MA = 0.10 ± 0.05 µ²; Mean Patient MVD = 1.92 ± 0.95%.

gain of ≥ 6.8 kg (15 lbs) within the previous year, alopecia, and generalized muscular weakness in his arms, legs, and back. He also complained of recurrent and localized back pain.

Blood Measurements. Blood samples were then taken to identify TSH and FT_4 levels to confirm the presence of subclinical hypothyroidism (Table 1). Patients were instructed to refrain from nonsteroidal anti-inflammatory drugs (NSAIDS) for 5 days prior to biopsy.

Muscle Biopsy Procedure. Biopsied samples were taken from the vastus lateralis muscle, 25 cm proximal to the tibial tuberosity and 5 cm lateral to the midline of the femur from each of the 4 patients.[7] The tissue was immediately placed in cold (4°C [39.2°F]) paraformaldehyde and 1.4% gluteraldehyde in 0.1M sodium cacodylate buffer. The tissue was cubed for light and electron microscopic evaluation and post fixed in osmium tetroxide in sodium cacodylate buffer. Following buffer rinses and dehydration in ethanol and propylene oxide, the tissues were flat embedded in Epon 812 and placed in a 70°C (158°F) oven to polymerize for 48-hours. Thick and ultrathin sections were cut using a Dupont Sorval MT2B ultramicrotome and prepared for light and electron microscopic analysis using standard procedures.[8]

Morphological Analyses. Qualitative light microscopy was performed using an Olympus BX51 light microscope with an Olympus DP11 digital camera. Digital images were analyzed using Image J and NIH Image analysis software. Electron microscopic examination was performed using a Philips 301 transmission electron microscope (TEM) equipped with an Advanced Microscopy Techniques image capturing system at magnifications from 4,500x to 45,000x, allowing for a more expansive examination of the muscle fiber.

Quantitative mitochondrial analysis was performed using Media Cybernetics, Inc. (Silver Springs, MD) Image-Pro Express image analysis software. Digital images were captured using a 1024 x 768 capture resolution setting using the Lumenera Scientific Infinity 2 side-column mounted digital camera. Each digital micrograph was then analyzed using the Image-Pro Express software.

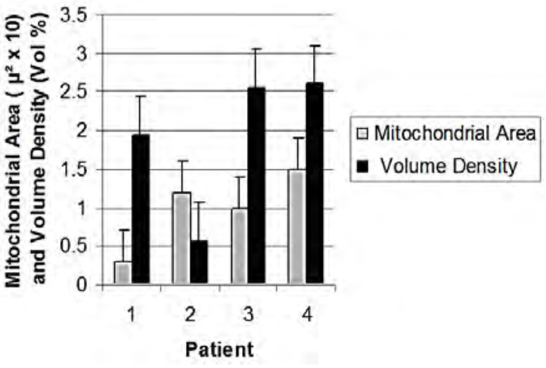


Figure 1. Comparison of mitochondrial area and volume density of four subclinical hypothyroid patients.

A grating replica calibration grid (Electron Microscopy Services, Hatfield, PA) in conjunction with a Photomicrographic Scale Marker (Dunn and Reidman, Pacific Palisades, CA) were used to calibrate the determined perimeter of each mitochondrion and to convert measurements from pixels to micrometers (ì). Ten captured electron micrographs per subject, each taken from different fibers, were analyzed to determine mitochondrial perimeter (MP). Mitochondrial area (MA) was calculated as a function of perimeter. Mitochondrial volume density was

Mitochondrial area (MA) was calculated as a function of perimeter. Mitochondrial volume density was measured using a 110 point lattice grid and applying the stereological procedures of Weibel.[9]

Results

Morphological Analysis. Microscopic analysis of skeletal muscle from these patients revealed focal areas of marked fiber size variation and atrophy, regions of myofibrillar disarray, and degeneration as well as widened intermyofibrillar regions. Areas of sarcolemmal blebbing, indicating a loss in membrane integrity, thickening, and lamination of the basement membrane were observed. Regions with occluded capillaries and areas with distended perivascular spaces filled with material of low electron density containing an infiltrate of red blood cells, macrophages, and lymphocytes were observed. Pyknotic nuclei as well as central nuclear migration, particularly in type II atrophic fibers, as well as Z-band streaming and disintegration, and areas devoid of myofilaments were observed. An increased concentration of glycogen aggregates and lipid deposits was obvious, particularly in type II fibers. Reduced numbers of mitochondria, many with disorganized membranes and cristae of unusual configurations, were observed (Figure 2). Vesicular structures adjacent to Z bands, intracytoplasmic inclusions, and lipofuscin granules were observed throughout but predominantly within subsarcolemmal and perinuclear regions.

Clinical and Morphometric Analyses. TSH, FT$_4$, and clinical symptoms of the 4 patients are shown in Table 1. Patients 1 and 2 had higher blood TSH values when compared to patients 3 and 4. Also, the skeletal muscle mitochondrial densities of patients 1 and 2 (Table 2) were lower when compared with patients 3 and 4.

Mitochondrial mass per unit of muscle fiber area is a morphological indicator of muscle oxidative capacity and can be expressed by measuring mitochondrial area and mitochondrial density in the same micrograph. Figure 1 shows graphic illustrations of mitochondrial mass per unit area of skeletal muscle mass. This was determined by measuring mitochondrial volume density in combination with mean mitochondrial area for the 4 patients. Patients 3 and 4 had a greater mitochondrial mass per unit area of muscle mass than did patients 1 and 2. Smaller sized mitochondria were evident in the skeletal muscle of patient 1 in comparison to the other three.

Discussion

The relationship between TSH levels and clinical symptoms in patients with subclinical hypothyroidism is variable and is thus of restricted diagnostic utility. This is illustrated by the cases reported in this study. For example, patient 2 had the highest TSH level (15.2 m IU/L) but did not complain of myalgia and reported no other hypothyroid symptoms (Table 1). In contrast, patient 4 complained of myalgia, reported symptoms compatible with overt hypothyroidism (Table 1), but had a lower TSH level (11.01m IU/L). This represents an example where morphological analysis offers a more objective measurement of disease progression.

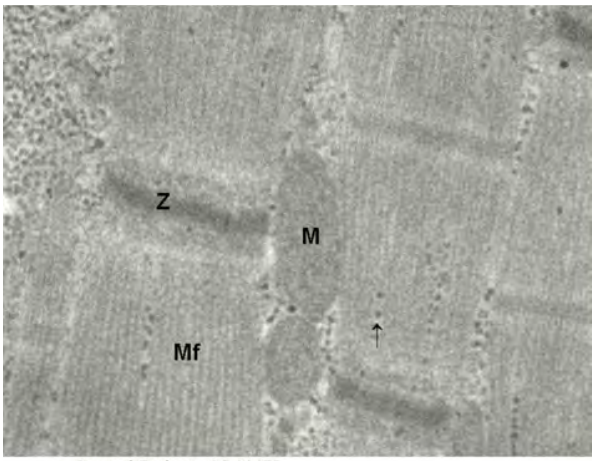
Myalgia is a consistent clinical hypothyroid symptom and often is a precursor to a decline in physical activity and exercise tolerance.[10,11,12] An early investigation of hypothyroid skeletal muscle identified areas of normal muscle that were interrupted by segments of complete structural disorganization characterized by myofilament loss.[13] Subsequent studies confirmed these results and thus established a relationship between myalgia due to overt hypothyroidism and skeletal muscle morphological changes.

Recognizing that specific skeletal muscle alterations are typical of hypothyroid patients, we examined skeletal muscle for histological changes that occur during subclinical hypothyroidism prior to its progression to overt hypothyroidism. We propose that the appearance of characteristic skeletal muscle "markers" would provide support for earlier intervention and perhaps a more efficacious treatment regimen.

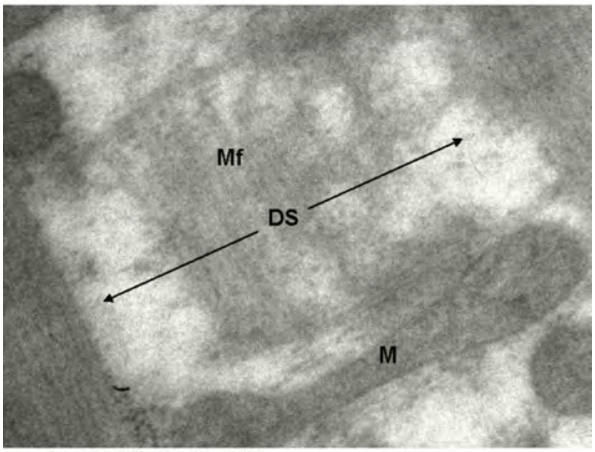
Table 2 indicates that the mitochondrial mass (mitochondrial area or mitochondrial volume density) in 2 of our 4 patients is smaller compared to normal skeletal muscle (mitochondrial area = 0.1ì ^{2}).[14] The number, size, and volume fraction of mitochondria closely reflect the metabolic capacity of the organism. Therefore, our data suggest that altered skeletal muscle metabolism is a prominent feature in the subclinical hypothyroid patient.

It is interesting to note that the 2 patients with elevated TSH levels (1 and 2) exhibited a low mitochondrial area per muscle fiber area (Figure 1) due to either an unusually low mean mitochondrial area (Patient 1 in Table 2) or a low mitochondrial volume density (Patient 2 in Table 2). In contrast, the 2 patients with lower TSH levels had mean mitochondrial

Figure 2. Ultrastructural comparison of a control (a) and a subclinical hypothyroid patient (sHT) (b).



a. Control Patient 25,000X



b. sHT Patient 4 25,000X

Fig. 2a. Control biopsy taken from an earlier unpublished study. Z bands (Z), mitochondria (M) and myofilaments (Mf) show good integrity. Small black dots are glycogen (↑) particles.

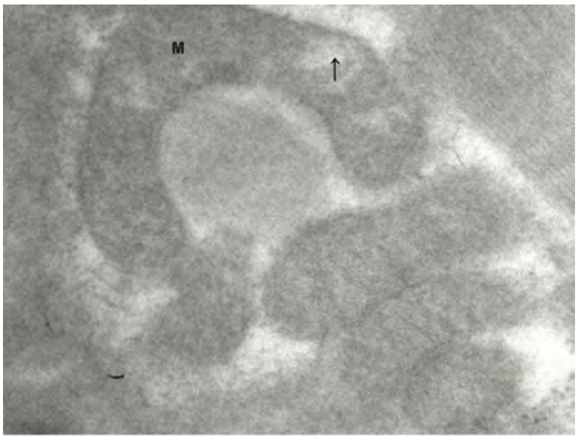
Fig. 2b. Skeletal muscle taken from patient 4. Note the damaged sarcomere (DS) displaying sparce myofilaments (Mf) with elongated mitochondria (M) spanning across the sarcomere space, once occupied by Z bands.

areas and densities closer to those for healthy adults (range is 0.088 ì ^{2} -0.155 ì ^{2}).[15]

In an earlier study, we measured mitochondrial area in patients with heart failure prior to (mitochondria area = 0.036 ì ^{2}) and following (mitochondrial area = 0.046 ì ^{2}) combined aerobic and resistance training.[16] We also measured mitochondrial area in postmenopausal women at baseline (0.039 ì ^{2}) (unpublished data). Other authors reported a mitochondrial area of 0.076 ì ^{2} (obese), 0.063 ì ^{2} (diabetic), and 0.114 ì ^{2} (lean adults) in muscle biopsies.[17] The mean mitochondrial area from the subclinical hypothyroid patients in this study (0.10 ± 0.05 ì ^{2}) was within a range of 0.03 ì ^{2} to 0.15 ì ^{2} (Table 2). This indicates that although mitochondrial area in subclinical hypothyroid patients did not differ greatly from healthy adults, it did demonstrate a tendency to decrease as TSH levels increased. The larger than expected mean mitochondrial area in our patients may be due to the high frequency of enlarged and distorted mitochondria (Figure 2 and Figure 3) often referred to as megamitochondria.[16,17] These very large mitochondria with low inner membrane density may be undergoing apoptosis. However, mitochondrial area in the subclinical hypothyroid patients did demonstrate a tendency to decrease as TSH levels increased (Table 1 and Table 2), suggesting that specific mitochondrial changes in skeletal muscle are reflective of increased TSH levels. These data are in contrast to another investigation that reported the presence of mitochondrial alterations only in prolonged clinical cases.[18]

The skeletal muscle histological profile of subclinical hypothyroidism was found to include focal areas of marked fiber variation and atrophy, regions of myofibrillar disarray, degeneration, and central nuclear migration, predominantly in type II fibers, regions devoid of myofilaments, Z band streaming and disintegration. Other studies involving overt hypothyroid patients reported “cores” of myofibrillar disarray in type I fibers, and this was observed to correlate with the severity and duration of hypothyroidism.[19,20,21] Increased concentrations of glycogen aggregates was observed in type II fibers occupying up to ⅓rd of the cross-sectional area.[20] The aggregates are thought to result from derangements of glycogen metabolism and to be related to the severity of subclinical hypothyroidism.[22] These observations are consistent with other reported findings.[20,22] The skeletal muscle changes that characterize subclinical hypothyroidism in our report are consistent with a previous study reporting a disease-related metabolic shift toward anaerobic ATP production in subclinical hypothyroidism.[24]

Figure 3. Subclinical hypothyroid patient 4.



Skeletal muscle taken from patient 4. Several mitochondria (M) have moved from their normal position between myofibrils (see Fig. 2) to within a sarcomere. They appear large, elongated and irregular in shape with a lower density of inner membranes. The curved mitochondria has lost some internal membrane structure (↑), suggesting that apoptosis may be taking place.

Mitochondrial plasticity is a response to changing metabolic conditions.[3,8,23,24] We observed reduced numbers of mitochondria, many with loss of membrane integrity, containing dense lipid inclusions and cristae of unusual configurations. These observations are consistent with previous studies of hypothyroid patients[10,19,22] and lend further support to the theory that thyroid hormones have a profound effect on mitochondrial energy expenditure.[25]

We also found areas containing pyknotic nuclei and central nuclear migration, consistent with severe hypothyroid myopathy,[26] as well as regions demonstrating a loss in sarcolemmal integrity and blebbing,[18,27,28] along with inflammatory cell infiltration into necrotic fiber areas. This contrasts with other studies where necrotic muscle fibers were found in the absence of interstitial inflammatory cells.[13]

In patients with severe hypothyroidism, selective type II fiber atrophy was reported to be due to impaired glycogen utilization and accompanied by an increased type I fiber area which gives the muscle a “bulky” appearance.[27,29] A link between the severity of myopathic symptoms, the degree of type II fiber atrophy and loss, and increased central nuclear displacement has been recognized.[22] A correlation between clinical severity of hypothyroidism and the degree of myofibrillar loss and abnormal glycogen accumulation has been established.[18] These observations are consistent with our report.

This report identifies specific skeletal muscle morphological changes that are characteristic of subclinical hypothyroidism. Establishing consistent morphological markers of subclinical hypothyroidism prior to disease progression could justify an earlier, more efficacious treatment with thyroid hormone. This treatment strategy may diminish morbidity by preventing disease progression from subclinical to overt hypothyroidism. Earlier initiation of this therapy may ultimately translate into an improvement in patients' lifestyle. Further research to establish reproducibility and clinical effectiveness appears to be warranted from these case studies.

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Address for reprint requests and other correspondence: Dr. Thomas G. Manfredi, PhD, Department of Kinesiology, University of Rhode Island, 101 Independence Square, 25 West Independence Way, Kingston, RI 02881. Phone: 401-874-5439; email: tma0868u@postoffice.uri.edu.

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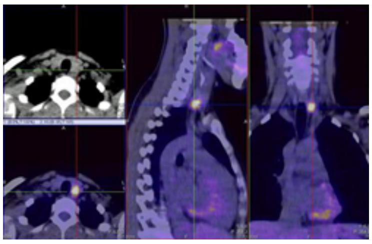

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FDG-PET/CT Visualizes a Case of Primary Hyperparathyroidism in a Patient with Gastrointestinal Stromal Tumor

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Laura Evangelista,[1,2] Anna Rita Cervino,[1]
Michele Gregianin,[1] Giorgio Saladini[1]

[1]Department of Radiotherapy and Nuclear Medicine Service,
Istituto Oncologico Veneto, Padova, Italy.
[2]Department of Biomorphological and Functional Sciences,
University Federico II, Napoli, Italy

**Correspondence author*: Laura Evangelista
Istituto Oncologico Veneto, IOV, I.R.C.C.S., Via Gattamelata, 64, 35128 Padova, Italy
Tel: +39 3396687579; Fax: +39 049 821 2205 laura.evangelista@tin.it

***Abstract*. Background.** Positron emission tomography/computed tomography (PET/CT) is used in clinical practice above all other tests to define the status of oncological disease. The predominant use of PET/CT is due to its use of 18F- fluorodeoxyglucose (FDG) to map cellular glucose metabolism. Some benign clinical conditions are also detected with FDG-PET/CT. These include inflammatory or hypermetabolic processes. Parathyroid adenoma is the most common cause of primary hyperparathyroidism, and nuclear medicine is already used to locate adenomas and to guide surgery for their removal. The utility of PET/CT with 11C-methionine for parathyroid disorders is well-documented in the research literature, while the usefulness of PET/CT with 18F-FDG is not clear. Case Presentation. We reported a case of a patient without specific symptoms for primary hyperparathyroidism, with a borderline high value of parathyroid hormone and a positive finding of parathyroid disease with PET/CT using 18F-FDG. Conclusion. PET/CT with 18F-FDG is useful in identifying parathyroid adenomas, and the techniques can be used to precisely clarify the nature of suspected nodules close to thyroid gland.

Keywords • Adenoma • Computerized tomography • 18F-Fluorodeoxyglucose • 11C-Methionine • Oncological disease • Parathyroid hormone • Parathyroidism • Positron emission tomography

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Case Reports

FDG-PET/CT Visualizes a Case of Primary Hyperparathyroidism in a Patient with Gastrointestinal Stromal Tumor

Laura Evangelista,[1,2] Anna Rita Cervino,[1]
Michele Gregianin,[1] Giorgio Saladini[1]

[1]Department of Radiotherapy and Nuclear Medicine Service,
Istituto Oncologico Veneto, Padova, Italy.
[2]Department of Biomorphological and Functional Sciences,
University Federico II, Napoli, Italy

Correspondence author: Laura Evangelista
Istituto Oncologico Veneto, IOV, I.R.C.C.S., Via Gattamelata, 64, 35128 Padova, Italy
Tel: +39 3396687579; Fax: +39 049 821 2205 laura.evangelista@tin.it

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***Abstract.* Background.** Positron emission tomography/computed tomography (PET/CT) is used in clinical practice above all other tests to define the status of oncological disease. The predominant use of PET/CT is due to its use of ^{18}F- fluorodeoxyglucose (FDG) to map cellular glucose metabolism. Some benign clinical conditions are also detected with FDG-PET/CT. These include inflammatory or hypermetabolic processes. Parathyroid adenoma is the most common cause of primary hyperparathyroidism, and nuclear medicine is already used to locate adenomas and to guide surgery for their removal. The utility of PET/CT with ^{11}C-methionine for parathyroid disorders is well-documented in the research literature, while the usefulness of PET/CT with ^{18}F-FDG is not clear. **Case Presentation.** We reported a case of a patient without specific symptoms for primary hyperparathyroidism, with a borderline high value of parathyroid hormone and a positive finding of parathyroid disease with PET/CT using ^{18}F-FDG. **Conclusion.** PET/CT with ^{18}F-FDG is useful in identifying parathyroid adenomas, and the techniques can be used to precisely clarify the nature of suspected nodules close to thyroid gland.

Keywords • Adenoma • Computerized tomography • ^{18}F-Fluorodeoxyglucose • ^{11}C-Methionine • Oncological disease • Parathyroid hormone • Parathyroidism • Positron emission tomography

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Background

The pathogenesis of primary hyperparathyroidism is due to an adenoma in 85% of cases. In a small percentage of cases, hyperparathyroidism involves multi endocrine syndrome (MEN). The diagnosis of primary hyperparathyroidism is based on hypercalcaemia and elevated levels of parathyroid hormone.

The flow-chart for concluding that parathyroid pathologies are present begins with a biochemical evaluation and thereafter with diagnostic imaging. ^{99m}Tc-MIBI-guided detection of abnormal parathyroid glands in primary hyperparathyroidism has become a popular and effective technique, especially to allow the performance of minimal surgery.[1]

Combined positron emission tomography/computed tomography (PET/CT), using ^{11}C-methionine as the alternative radio-labelled amino acid tracer agent, has already been demonstrated to play an important role in localating pathological parathyroid glands.[2-5] On the other hand, Lange-Nolde et al. [6] suggested that PET with ^{18}F-DOPA (3-,4-dihydroxy-6-(18)-F-fluorophenylalanine), another radiolabelled tracer, is not useful in the detection of parathyroid adenomas in patients with primary hyperparathyroidism. Today, however, the role of ^{18}F-FDG PET/CT in identifying parathyroid pathologies is still not clear.

Case presentation

A 37-year-old female who had a history of gastrointestinal stromal tumor and was treated with surgery in July 2009 was referred to our Department of Nuclear Medicine for evaluation of the disease state. She underwent PET/CT exam for post-surgery evaluation. At the time of imaging, she reported hair loss, trembling hands, split nails, and irregular menstruation. The PET/CT examination performed with ^{18}F-FDG showed a small area near and posterior to the left lower pole of her thyroid gland. The small area was moderately hypermetabolic and had a maximum Semiquantitative Uptake Value (SUV max) of 6.0 (Figure 1A).

The biochemical evaluation showed a serum parathyroid hormone level of 76 ng/L (reference values 9-to-55 ng/L) and reference values of serum calcium and phosphate. For further evaluation, the patient underwent a neck ultrasound exam. This revealed the presence of an ipoechoic nodule with structural morphology similar to the parathyroid gland and in the same site.

Finally, based on clinical and diagnostic findings, a diagnosis of primary hyperparathyroidism was made. Thereafter, for the localization of the adenoma, a ^{99m}Tc-sestamibi parathyroid dual-phase scintigraphy was performed. This revealed an area with high uptake (Figure 1B) in the same place shown by the PET/CT images. These data demonstrate the utility of ^{18}F-FDG uptake in identifying the site of the adenoma.

Discussion

PET/CT with ^{18}F-FDG is an imaging modality that has been in widespread use in recent years. The procedure is used especially in the oncological field, but also in the cardiovascular and neurological fields. The increased glucose metabolism of all pathological processes can be visualized by FDG-PET.

Primary hyperparathyroidism is due mainly to adenomas of the parathyroid glands. The increased number of parathyroid cells elevates glucose metabolism. Parathyroid adenomas, as incidental findings are not often detected during PET examinations, but other incidental clinical conditions (e.g. breast cancer, thyroid cancer, colon inflammatory disease, etc.) are usually depicted.[7-9] In fact, the research literature contains only one case, by Kim et al.,[10] that demonstrated an intra-thyroidal parathyroid adenoma discovered by FDG-PET.

The patient whose case we report here had a history of GIST, a rare cancer that affects the digestive tract or nearby structures within the abdomen. Followup post-surgery evaluation was the reason the patient had an evaluation with FDG-PET/CT.

In the literature, Papillon et al.[11] reported a case of a patient with MEN-1 and associated GIST. They conjectured that the patient's GIST arose independently by a mechanism unrelated to the MEN-1 gene.

Precise identification of the location of a suspected nodule close to the thyroid gland can be useful in deciding whether or not further diagnostic tests are appropriate. Such decisions are particularly important in the management of oncological patients. The reason is that it is well known that oncological pathologies can induce a hypercalcaemia, as can parathyroid adenomas. It is necessary, then, to differentiate between oncological pathology and parathyroid adenomas as the source of patients' hypercalcemia.

Conclusion

Should ^{18}F-FDG be used as an alternative to ^{11}C-methionine to detect parathyroid adenomas? In view of the clinical flow-chart, this is questionable for two reasons,: first is the cost/benefit ratio, as PET/CT is more expensive than other imaging modalities; second is the proved diagnostic utility of scintigraphy with ^{99}Tc-sestamibi. Far more data from studies are necessary to clearly delineate the advantages of FDG-PET/CT compared to other procedures in the diagnosis of primary hyperparathyroidism. However, nowadays, FDG-PET/CT is considered the best technique for oncological evaluations, and in the near future, it may become clear that this imaging technique also could be employed in the diagnosis of other clinical conditions including parathyroid adenomas.

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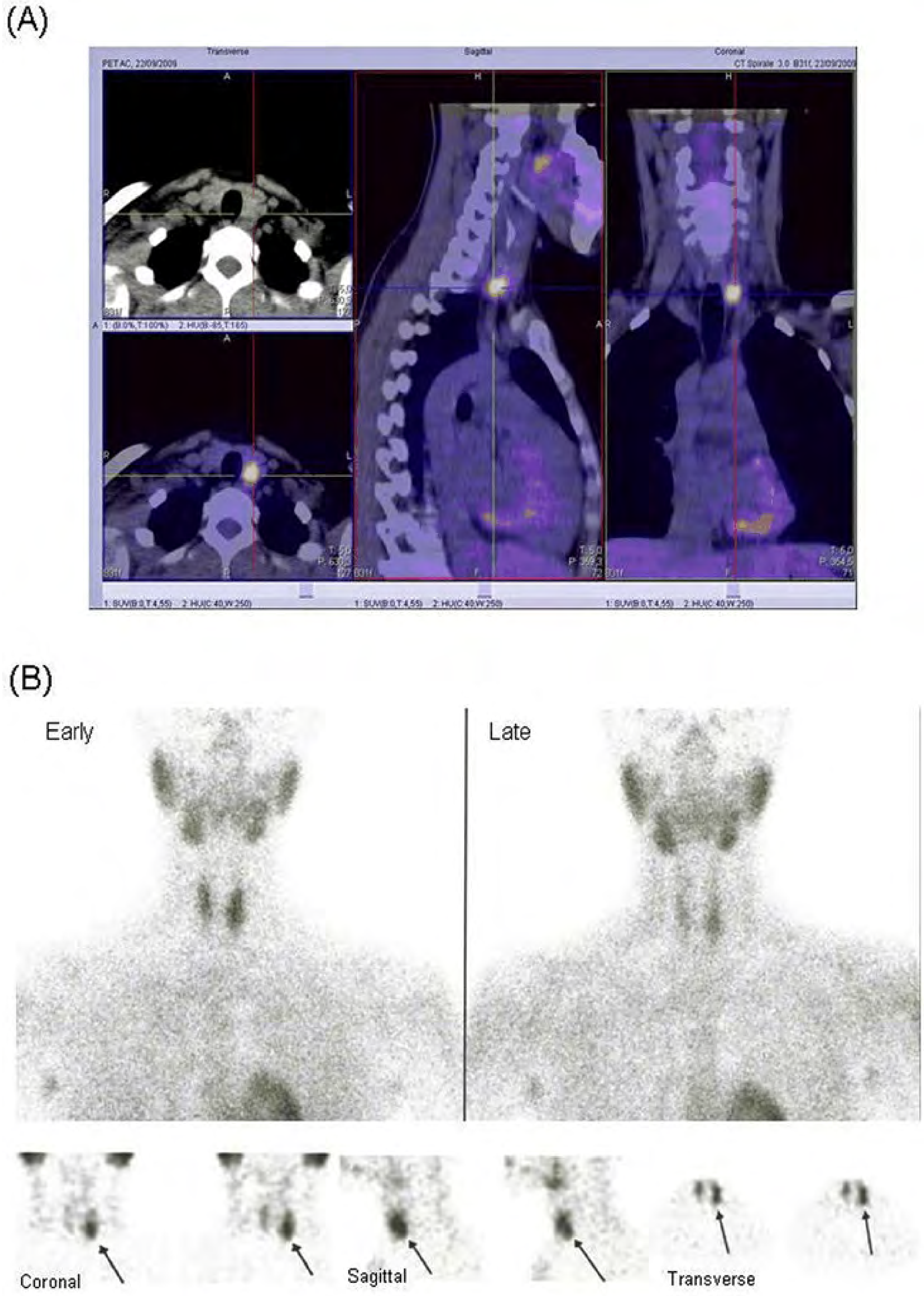

Figure 1. (A) PET/CT image with the use of ^{18}F-FDG. It shows a small area near and posterior to the left lower pole of the thyroid gland with moderate hypermetabolism. (B) Depiction of the localization of the adenoma shown by ^{99m}-Tc-sestamibi parathyroid dual-phase scintigraphy.

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Thyroid Science 3(6)CR1-3, 2008

Utility of Adrenal Cortical Scintigraphy with ^{131}I-6-β-Methyl-Norcholesterol in a Case of Mismatch Between Morphological and Functional PET Imaging

(Full Text Free in pdf format)

Laura Evangelista,* Teresa De Falco,* Carmine di Nuzzo, Marco Salvatore

*Department of Biomorphological and Functional Sciences
University Federico II, Via S. Pansini, 5, I-80131 Napoli, Italy

Contacts: laura.evangelista@tin.it & teresadefalco@yahoo.it

Introduction

John C. Lowe, MA, DC: Editor-in-Chief

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We are pleased to publish this case report by Evangelista, De Falco, di Nuzzo, and Salvatore. These Italian physicians describe a patient whose presenting complaint was abdominal pain but who was then found to have an adrenal cortical adenoma.

Many clinicians who correspond with us at *Thyroid Science* ask if we will publish papers on adrenal dysfunctions. As these disorders are so often related to thyroid dysfunction, our answer has been yes. According to our communications, most clinicians find that their thyroid patients have cortisol deficiencies, yet others have unexplained elevated cortisol levels.

The patient of Evangelista et al. had elevated renin rather than cortisol. They found the source to be an adrenal cortical "incidentaloma." An incidentaloma is an unexpected finding of an adenoma during a diagnostic procedure performed to learn the source of a patient's abdominal symptoms.

The authors performed adrenal scintigraphy using "NCL-6-I." NCL-6-I is a radioactive agent taken up by the adrenal glands some ten-times more than alternative agents.[1] By measuring its accumulation in the adrenal gland by scintigraphy, it functions as an effective radioactive tracer. Resulting scintigrams are the photographic record that indicates the intensity and distribution of radioactivity in parts of the adrenal glands after the diagnostician administers the radioactive tracer. The authors provide three such scintigrams. They note that adrenocortical radiocholesterol scintigraphy, in which they used NCL-6-I, is the most accurate non-invasive imaging technique in differentiating benign cortical adenomas from space-occupying or destructive adrenal lesions. They point out that the faint uptake of the tracer in the patient indicated an adrenal cortical adenoma.

We would especially like to note a precaution from the authors. That is, in the population at large, adrenal adenomas are fairly common, ranging between 2% and 9%. The authors emphasize the importance of the incidental detection of such adrenal lesions, especially for the patient with a previous malignancy.

This case report is one of the few published since 1996 on the value of adrenal scintigraphy with NCL-6-I. We are proud to add this case report to the literature on this tracer. We believe that knowledge of the diagnostic procedure will be of value to some clinicians trying to determine why some patients have high adrenocortical hormone levels—especially high cortisol levels not explained by common mechanisms such as pain, inflammation, glycemic dysregulation, or psychologically-induced stress.

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Key Words. Adrenal cortex • Computed tomography • ^{131}I-6-ß-methyl-Norcholesterol • Incidentalomas • Scintigraphy •

Evangelista, L., Teresa De Falco, T., Carmine di Nuzzo, C., Salvatore, M.: Utility of adrenal cortical scintigraphy with ^{131}I-6-β-Methyl-Norcholesterol in a case of mismatch between morphological and functional PET imaging. *Thyroid Science*, 3(6):CR1-3, 2008.

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Laura Evangelista,* Teresa De Falco,*
Carmine di Nuzzo, Marco Salvatore

*Department of Biomorphological and Functional Sciences
University Federico II, Via S. Pansini, 5, I-80131 Napoli, Italy

Contacts: laura.evangelista@tin.it & teresadefalco@yahoo.it

Abstract: We present a clinical case showing the role of adrenal cortical scintigraphy with ^{131}I-6-β-Methyl-Norcholesterol in a patient with an incidental adrenal cortical mass presenting mismatch between morphological, functional, and PET imaging.

Keywords: Adrenal cortex • Computed tomography • ^{131}I-6-β-methyl-Norcholesterol • Incidentalomas • Scintigraphy

Introduction

The rate of finding unexpected adrenal masses, so-called “incidentalomas,” has been rising because of increased use of CT, MRI, and ultrasound to study symptoms potentially originating from the abdomen.[1] Incidental adrenal masses are identified in approximately 5% of abdominal CT scans[2] and in up to 8.7% of autopsies.[3]

In patients without a known malignancy, most of these masses represent adrenal adenomas.[4] Here we describe a case of an adrenal cortical mass showing volumetric increase at CT imaging, low ^{18}F-FDG uptake at PET/CT, and a positive result at adrenal scintigraphy with ^{131}I-6-β-Methyl-Norcholesterol (NCL-6-I).

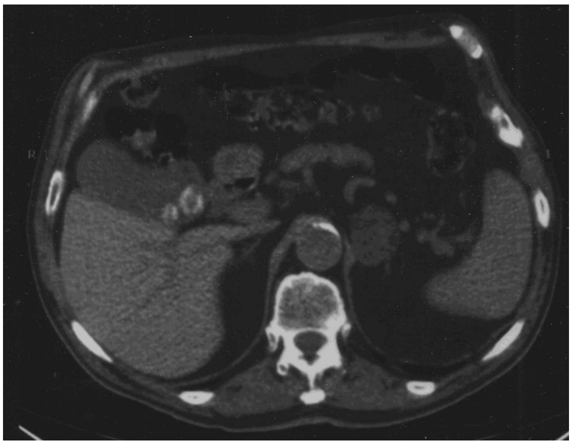

Figure 1

Case Report

A 77 year-old man was admitted to our hospital for the presence of abdominal pain. He had arterial hypertension, family history of cancer, and negative oncological laboratoristic markers (CEA, α-FP, Ca19-9, TPS). An abdominal ultrasound showed an ipoechoic mass in the left adrenal lodge with regular boundaries confirmed by a contrast enhanced (c.e.) computed tomography (CT) (diameter of 3.5 cm). After five months a non c.e. CT revealed an incremental diameter (4.2 cm vs 3.5 cm), which was suspicious for a malignant adrenal mass (Fig.1). ^{18}F-FDG PET/CT performed one month later showed low tracer uptake (SUV max 2.1) in the adrenocortical mass (Fig.2). Biochemical evaluation (aldosterone, cortisol, testosterone, androstenedione, DHEA-S, and renin) showed only an increment of plasmatic renin, both orthostatic and supine dosage [57.5 pg/ml (normal value 1.8-33.0 pg/ml) and 25.8 pg/ml (normal value 1.3-16.0 pg/ml), respectively]. On the basis of CT and PET/CT findings, an NCL-6-I adrenal scintigraphy was performed. The NCL-6-I scan showed left adrenal gland increase tracer uptake with faint controlateral uptake indicating a left adrenocortical adenoma (Fig.3).

Discussion

The diagnostic algorithm to be adopted in patients with incidentalomas is still somewhat controversial in the literature. However, once those lesions with an obvious radiological diagnosis (e.g. simple cyst, myelolipoma) are excluded, the diagnostic approach to incidentalomas should comprise the following steps: (1) obtain an accurate clinical and biochemical profile to be certain of the functional status of the lesion, and (2) make a differential diagnosis of benign versus malignant.[5][6][7]

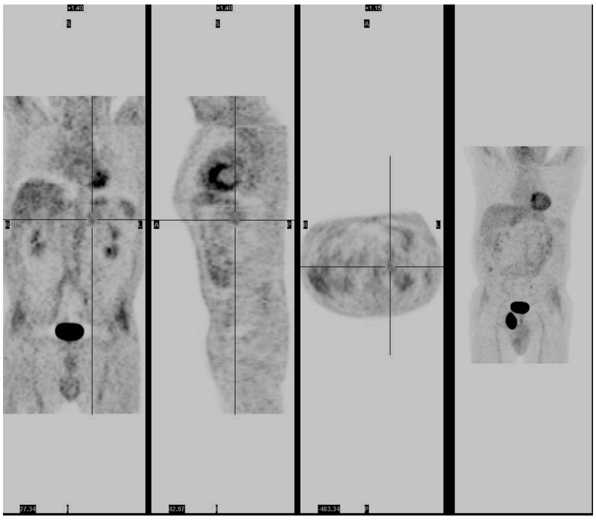

Figure 2

Because adrenal adenomas are relatively common (2%-to-9%) in the general population, an incidental detection of such lesions poses a diagnostic challenge, particularly in patients with a previous clinical history of malignancy.[3][8][9][11] Among high-resolution anatomic imaging techniques, CT is used as the first-line diagnostic modality for screening and determining the nature of the adrenal lesions, and MRI is often performed to further characterize indeterminate masses seen on CT. Serial CT imaging has been used, since lesions showing a progressive growth are more likely to be malignant.[6][12] Recently, ^{18}F-FDG PET has also shown great potential in differentiating malignant from benign adrenal lesions in patients with proven malignancy, or in patients with incidentally detected adrenal tumors on CT or MRI studies.[13][14][15] However, even with increasing experience in the evaluation of adrenal lesions using ^{18}F-FDG PET, it is not fully understood why some adenomas show increased tracer uptake and some do not. It has been suggested that the functional state of an adenoma is a factor determining the intensity of uptake, with ^{18}F-FDG uptake being increased in functioning adrenal masses.[16]

Adrenocortical radiocholesterol scintigraphy has been shown to be the most accurate non-invasive imaging technique in differentiating benign cortical adenomas from space-occupying or destructive adrenal lesions.[5][17][18] Maurea et al. reported a positive predictive value of 89% and a negative predictive value of 100% in ruling out malignancy of the adrenal mass using NCL-6-I imaging.[10] An English language Medline search from January 1996 to April 2008 produced few papers on the incremental value of adrenal scintigraphy with NCL-6-I.

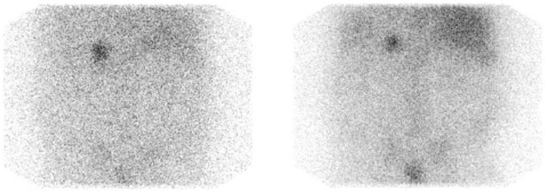

Figure 3

The clinical case reported here confirms that adrenal cortical scintigraphy with ^{131}I-6-β-methyl-Norcholesterol may play a role in the diagnostic algorithm of incidentalomas when the diagnostic work-up shows a mismatch between morphological (increasing in volumetric pattern) and functional PET data (low FDG uptake).

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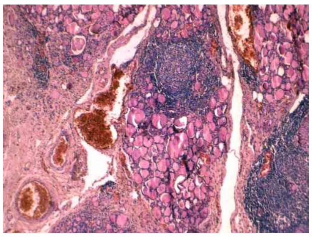
Histology: Hashimoto's thyroiditis

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Development of Postpartum Graves' Hyperthyroidism in a Woman with Hashimoto's Hypothyroidism

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Cindy Huang, MD, Diane Fresca, MD
Dragana Jokic, MD, and Xiangbing Wang, MD, PhD

Division of Endocrinology, Metabolism & Nutrition, Department of Medicine,
UMDNJ- Robert Wood Johnson Medical School, New Brunswick, NJ 08093-0019

Corresponding author: Xiangbing Wang, MD, PhD FACE
Division of Endocrinology, Metabolism & Nutrition
Robert Wood Johnson University Hospital-UMDNJ
MEB 384B, 1 RWJ Place, P.O.box 19. New Brunswick, NJ 08903
Phone (732) 235-7751 Fax (732) 235-7069 E-mail: wangx9@umdnj.edu

Abstract. Transformation of Hashimoto's hypothyroidism to Graves' hyperthyroidism is extremely rare, but does occur. The course and severity of autoimmune thyroid diseases are altered during pregnancy and the postpartum period. We report the clinical course, laboratory findings, and treatment of a female patient with Hashimoto hypothyroidism. She had a past medical history of Hashimoto hypothyroidism and had been on LT4 replacement therapy for two years. Six-months postpartum, however, she developed Graves' hyperthyroidism. LT4 was discontinued, and the patient was started on methimazole, 30 mg daily. Methimazole was discontinued one month later due to severe side effects, and 131 radioiodine therapy was applied. We suggest that patients with preexisting Hashimoto's hypothyroidism are not immune to developing Graves' disease. When such patients have unexpected symptoms and changes in thyroid function tests, especially during pregnancy or in the postpartum state, this unlikely diagnosis should be entertained and treated accordingly.

Keywords • Autoimmune thyroid disease • Graves' disease • Hashimoto's • Hyperthyroidism • Hypothyroidism • LT4 • Methimazole

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Case Reports

Development of Postpartum Graves' Hyperthyroidism in a Woman with Hashimoto's Hypothyroidism

Cindy Huang, MD, Diane Fresca, MD
Dragana Jokic, MD, and Xiangbing Wang, MD, PhD

Division of Endocrinology, Metabolism & Nutrition, Department of Medicine,
UMDNJ- Robert Wood Johnson Medical School, New Brunswick, NJ 08093-0019

Corresponding Author: Xiangbing Wang, MD, PhD FACE
Division of Endocrinology, Metabolism & Nutrition
Robert Wood Johnson University Hospital-UMDNJ
MEB 384B, 1 RWJ Place, P.O.box 19. New Brunswick, NJ 08903
Phone (732) 235-7751 Fax (732) 235-7069 E-mail: wangx9@umdnj.edu

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Abstract. Transformation of Hashimoto's hypothyroidism to Graves' hyperthyroidism is extremely rare, but does occur. The course and severity of autoimmune thyroid diseases are altered during pregnancy and the postpartum period. We report the clinical course, laboratory findings, and treatment of a female patient with Hashimoto hypothyroidism. She had a past medical history of Hashimoto hypothyroidism and had been on LT_4 replacement therapy for two years. Six-months postpartum, however, she developed Graves' hyperthyroidism. LT_4 was discontinued, and the patient was started on methimazole, 30 mg daily. Methimazole was discontinued one month later due to severe side effects, and 131 radioiodine therapy was applied. We suggest that patients with preexisting Hashimoto's hypothyroidism are not immune to developing Graves' disease. When such patients have unexpected symptoms and changes in thyroid function tests, especially during pregnancy or in the postpartum state, this unlikely diagnosis should be entertained and treated accordingly.

Keywords Autoimmune thyroid disease • Graves' disease • Hashimoto's • Hyperthyroidism • Hypothyroidism • LT_4 • Methimazole

Introduction

Hashimoto thyroiditis and Graves' disease are the most two common autoimmune thyroid diseases. They are generally thought to be discrete entities. The autoantibodies thyroid peroxidase (TPO) and thyroglobulin (Tg) are the classic markers of Hashimoto's thyroiditis, a condition in which thyroid lymphocytic infiltration and thyrocyte damage may progress to hypothyroidism.

Graves' disease is caused by autoantibodies that induce thyrotoxicosis by mimicking the action of TSH and activating the TSH receptor. Reports showed that antibodies that either stimulate or block TSH receptors in Graves' disease patients were present in concentrations similar to those in Hashimoto thyroiditis.[1] Studies also show a link between Graves' disease and Hashimoto thyroiditis.[2]

The course and severity of autoimmune thyroid diseases are altered during pregnancy and the postpartum period. The thyroidal response to a fluctuating immune status, combined with changes in thyroid economy during pregnancy, may result in a need to adjust the treatment regimen for thyroid disease during pregnancy. These and other not yet completely elucidated factors lead to partial tolerance and a dominant T-helper subset 2 (Th2) immune profile, which explains the positive influence of pregnancy on the clinical course of many (albeit not all) autoimmune diseases and, characteristically, the generalized improvement of thyroid autoimmune diseases during pregnancy.

Patients with Hashimoto's hypothyroidism who are on thyroid hormone replacements are frequently observed to have an increased requirement for levothyroxine early in pregnancy. This, however, is not true of all patients.[3,4]

Graves' disease usually improves during pregnancy but flares up after delivery. Due to the profound autoimmune modifications that occur post-delivery, it is understandable that the postpartum period has been associated with a greater frequency of onset, recurrence, or exacerbation of thyrotoxicosis from Graves' disease and postpartum thyroiditis.[5] Spontaneous conversion from hypothyroidism to hyperthyroidism, although not common, has been reported before.[6-10] Development of Graves' disease in the first trimester of pregnancy and later stages of pregnancy has also been reported.[8,10,11]

Spontaneous transformation from Hashimoto hypothyroidism to postpartum Graves' hyperthyroidism , however, has not previously been reported. We report a patient with a 2-year history of Hashimoto hypothyroidism and replacement therapy who developed Graves' hyperthyroidism 6- months postpartum.

Case Presentation

A 34-year-old female presented to the emergency department with complaints of palpitations and dizziness that was worsening. Three months previously, she had undergone a work up for fatigue following a miscarriage in June 2005. At that time, her TSH was < 0.1 mIU/L, her free T_4 was within range at 1.0 ng/dL, and her 123 Iodine uptake and scan showed a 6-hour RAI uptake of 9.7% and 24-hour RAI uptake of 13% with patchy and heterogeneous activities. The patient was sent to an endocrinologist for evaluation.

After five months of observation, when her TSH rose to 32 mIU/L and her free T_4 dropped to 0.8 ng/dL, the patient was diagnosed with Hashimoto's thyroiditis.

Anti-TPO antibodies at that time were positive at 67.7 IU/mL. Two months after initiation of treatment with LT_4, 100 µg daily, her TSH dropped to 0.032 mIU/L and her free T_4 elevated to 2.13 ng/dL. Her LT_4 dose was subsequently decreased to 50 µg daily. Two months later, the patient became euthyroid and remained stable until becoming pregnant in August 2006.

During her first trimester, her TSH rose to 98 mIU/L and her LT_4 was increased back to 100 µg daily. However, her thyroid function tests again normalized, and she remained euthyroid through her third trimester. She had an uncomplicated delivery. Postpartum, she remained on 100 µg of LT_4 until she presented to her endocrinologist on September 2007 with symptoms of thyrotoxicosis.

At this time, her TSH was undetectable and her free T_4 was markedly elevated at 10.44 ng/dL. A 123 iodine uptake and scan revealed a homogenous 4-hour uptake of 66% and a 24-hour uptake of 73%. LT_4 was discontinued, and the patient was started on methimazole, 30 mg daily.

The patient's thyrotoxic symptoms persisted four weeks after she initiated methimazole, and she developed skin rashes, nausea, dizziness, and had episodes of syncope. Because of this, she sought treatment at our emergency department.

Table 1. Time course of TFTs, 123 Iodine uptake, thyroid antibodies and treatments.

Date	TSH	Free T_4	24 hour RAI Uptake	TPO	TSI	LT_4 Dose
6/05	< 0.01	1.0	13%			None
10/05	31.19	0.8		67.7	Start	Start 100 µg
12/05	0.032	2.13				100 µg
2/06	0.009	1.79				100 µg
4/06	0.86	1.24				50 µg
7/06	0.71	1.31				50 µg
8/06 (1st trimester)	98.070	0.97				50 µg
9/07 (6 months post partum)	0.049	10.44	73%			100 µg, off T_4 and start Tapazole
10/07	< 0.01	2.02				Off Tapazole
11/07	< 0.01	1.03			357%	131RAI therapy
2/7/08	15.38	0.94				50 µg
4/7/08	0.288	1.23				88 µg
7/14/08	0.228	1.33				88 µg

Reference ranges: 123Iodine uptake, 24 hour 15-35%; TPO Ab, < 30 IU/mL; TSI, 0-129%; TSH, 0.35-5.50 mIU/mL; FreeT_4, 0.61-1.76 ng/dL.

Upon admission, her TSH was undetectable, her free T_4 was 2.02 ng/dL, and her thyroid stimulating immunoglobulin (TSI) level was elevated at 357%. Methimazole was discontinued due to her skin rashes and because she had transaminase elevations greater than two times the upper limit of normal. She was hydrated with intravenous fluid and administered propranolol and prednisone while waiting for 131 RAI therapy.

Seven days after discontinuing methimazole, the patient received 10 mCi of ^{131}I during her admission for definitive treatment. One month later at outpatient follow-up, the patient was found to be clinically euthyroid with a reference range free T_4. Three month later, however, the patient complained of fatigue, dry skin, and was found to be clinically hypothyroid. Her TSH was high at 15.38mIU/L, and her free T_4 was low in its reference range at 0.94 ng/dL. Treatment with LT_4 was then reinitiated (Table 1).

Discussion

Hyperthyroidism is known to occur early in the course of Hashimoto's thyroiditis and is commonly termed "Hashitoxicosis."[12] At this time, the inflamed thyroid gland leaks preformed hormone. In patients who have already entered the hypothyroid phase of Hashimoto's thyroiditis, the injured thyroid gland has lost its synthetic ability and the patient needs life long replacement therapy. Affected patients are not expected to subsequently develop hyperthyroidism.

In the case we report here, however, the clinical course and treatment are unique. The patient was initially noted to have subclinical hyperthyroidism with low ^{123}I uptake in June 2005, which indicated Hashitoxicosis. Four months later, she developed hypothyroidism and had elevated TPO antibodies. She began T_4 replacement therapy. This, of course, was the typical course for a patient with Hashimoto hypothyroidism.

During the first trimester of her pregnancy, her LT_4 replacement dose had to be increased. This indicated that she had reduced thyroid reserve because Hashimoto's thyroiditis had injured or destroyed her thyroid gland.

Six months postpartum, she developed typical signs and symptoms of hyperthyroidism. She was found to have a high ^{123}I uptake, high TSI titer, low TSH, and a high free T_4. These findings confirmed the diagnosis of Graves' hyperthyroidism.

The patient was treated with methimazole. However, she developed skin rashes and liver toxicity one month later. Because of this, Methimazole was discontinued and propranolol was used to control her hyperthyroidism while waiting for 131RAI therapy.[13,14]

Spontaneous conversion from hypothyroidism to hyperthyroidism, as in the patient we describe here, is not common, although it has been reported before.[6-11] Some of the described changes in clinical course that researchers have reported were associated with pregnancy or previous treatment with antithyroid medications; others occurred spontaneously. Nearly all of the patients in these cases expressed more than one type of thyroid auto-antibody concomitantly or over time. These observations are in accordance with a series of studies from the 1990's. These studies established that the same patient may express one or more different TSH receptor antibodies in addition to anti-TPO or anti-thyroglobulin antibodies.[15-17]

Factors influencing the relative concentrations of each antibody and how the different antibodies interact with one another are likely responsible for the prevailing clinical manifestations. Spontaneous transformation from Hashimoto hypothyroidism to Graves' hyperthyroidism postpartum, however, has never been reported before. The etiology of Graves' disease in a postpartum-patient already on replacement for Hashimoto's hypothyroidism remains to be elucidated at the present time.

Our patient had both positive TSI and positive TPO antibodies at two different points in her clinical course. She had Hashimoto hypothyroidism and had already been on replacement for two years. She also had a sufficiently reduced thyroid reserve to require an increase in LT_4 replacement during her first trimester of pregnancy. There should not have been enough thyroid hormone in reserve in her thyroid gland to respond to the stimulating antibodies postpartum.

Literature review revealed several case reports describing patients who transitioned from one form of autoimmune thyroid disease to another. [15-17] It appears that the course and severity of autoimmune thyroid disease are altered during or in the postpartum period. The pregnant woman's immune state may have changed from predominant anti-TPO antibody or thyroid-binding inhibiting immunoglobulin (TBII) to TSI.[16-18] Serum levels of TBII and TSI have been shown to consistently decrease or disappear during pregnancy and increase after delivery.[15-18] Progesterone (P) and estrogen (E) exert these immuno-modulating effects. Whereas progesterone decreases reactivity of both the humoral and cellular arms of the immune system, estrogen exerts opposite effects. Because pregnancy is characterized by an overall increase in the P:E ratio, the reactivity of both arms of the immune system is inhibited.[9] Thyroid autoantibodies and antibodies directed against other tissues are partially suppressed during pregnancy and are exacerbated after delivery. The precise mechanism of these immune effects remains obscure. Presumably, the rapid reduction in immune suppressor function of the P:E ratio following delivery leads to the reestablishment and exacerbation of these conditions.[20-22]

The postpartum rebound of thyroid autoimmune diseases is a striking example of this phenomenon.[22] We suggest that our patient had thyroid hormone in reserve in her thyroid gland for two reasons: her anti-TPO antibody level was low and did not completely destroy her thyroid gland, and her relatively low LT_4 dosage before pregnancy allowed thyroid hormone production to proceed. During her pregnancy and postpartum period, her autoimmune status changed predominant to TSI (359%). The antibodies may have stimulated her remaining thyroid gland to produce enough thyroid hormone to produce Graves' hyperthyroidism six months postpartum.

Conclusion

We report a case of Graves' hyperthyroidism that developed in a woman with Hashimoto's hypothyroidism six month postpartum. Transformation of Hashimoto's hypothyroidism to Graves' hyperthyroidism is extremely rare. However, patients with Hashimoto's hypothyroidism are not immune to the development of Graves' disease. When such patients have unexpected symptoms and changes in thyroid function tests that characterize hyperthyroidism, especially during pregnancy or the postpartum state, this unlikely diagnosis should be entertained and treated accordingly.

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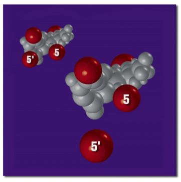

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Case Report: Hyperthyroidism, Iron-deficiency Anemia, and Celiac Disease

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Cindy Huang, MD, PGY3[1]
Amy Toscano-Zukor, DO[2]
Xiangbing Wang, MD, PhD[2]

[1]UMDNJ-Robert Wood Johnson Medical School, Department of Medicine,
One Robert Wood Johnson Place MEB 486, New Brunswick, NJ 08903-0019.

[2]UMDNJ-Robert Wood Johnson Medical School, Department of Endocrinology,
One Robert Wood Johnson Place MEB 384B, New Brunswick, NJ 08903-0019.

Contact: Dr. Cindy Huang, P: (908) 698-3988, F: (732) 422-1709, Cindy.Huang@gmail.com

ABSTRACT. The objective was to report a case of a woman with celiac disease presenting with hyperthyroidism and iron-deficiency anemia. **Methods**. We report the clinical course of this patient and her laboratory findings. We highlight the important associations between hyperthyroidism, iron-deficiency anemia, and celiac disease. The literature is reviewed for the typical and atypical presentations of celiac disease in relation to hyperthyroidism and iron-deficiency anemia. **Results**. A 37-year-old woman presented with symptoms of hyperthyroidism and was found to have iron-deficiency anemia. During the work up for iron-deficiency anemia, she was diagnosed with celiac disease on small-bowel biopsy. After being placed on a gluten-free diet, symptoms of hyperthyroidism improved without anti-thyroid medication. **Conclusion**. Our case demonstrates that routine screening for celiac disease should be highly considered for patients with both hyperthyroidism and iron-deficiency anemia. Treating celiac disease by gluten withdrawal may reduce morbidity and improve quality of life in patients with hyperthyroidism, anemia, and celiac disease.

Keywords. Celiac disease • Hyperthyroidism • Iron-deficiency anemia

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Case Report: Hyperthyroidism, Iron-deficiency Anemia, and Celiac Disease

Cindy Huang, MD, PGY3,[1] Amy Toscano-Zukor, DO,[2] Xiangbing Wang, MD, PhD[3]

[1]UMDNJ-Robert Wood Johnson Medical School, Department of Medicine,
One Robert Wood Johnson Place MEB 486, New Brunswick, NJ 08903-0019.

[2,3]UMDNJ-Robert Wood Johnson Medical School, Department of Endocrinology,
One Robert Wood Johnson Place MEB 384B, New Brunswick, NJ 08903-0019.

Correspondence: Dr. Cindy Huang, P: (908) 698-3988, F: (732) 422-1709, Cindy.Huang@gmail.com

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Abstract. The objective was to report a case of a woman with celiac disease presenting with hyperthyroidism and iron-deficiency anemia. **Methods.** We report the clinical course of this patient and her laboratory findings. We highlight the important associations between hyperthyroidism, iron-deficiency anemia, and celiac disease. The literature is reviewed for the typical and atypical presentations of celiac disease in relation to hyperthyroidism and iron-deficiency anemia. **Results.** A 37-year-old woman presented with symptoms of hyperthyroidism and was found to have iron-deficiency anemia. During the work up for iron-deficiency anemia, she was diagnosed with celiac disease on small-bowel biopsy. After being placed on a gluten free diet, symptoms of hyperthyroidism improved without anti-thyroid medication. **Conclusion.** Our case demonstrates that routine screening for celiac disease should be highly considered for patients with both hyperthyroidism and iron-deficiency anemia. Treating celiac disease by gluten withdrawal may reduce morbidity and improve quality of life in patients with hyperthyroidism, anemia, and celiac disease.

Keywords • Celiac disease • Hyperthyroidism • Iron-deficiency anemia

Introduction

Celiac disease is on the rise globally, particularly in the Western countries. Recent population screening studies have shown that the prevalence of celiac disease in Western countries approaches 1%.[1] The condition is greatly under-diagnosed due to its previously perceived rarity.[2,3] The incidence and failure to diagnose the condition can result in complications for the affected patient.[4] Many autoimmune diseases can be associated with celiac disease, including autoimmune thyroid disease. An association between thyroid disease and celiac disease has previously been described.[1,5,6,7,8] There is also an increased incidence of Graves' hyperthyroidism among patients with celiac disease, and researchers have recommended routine screening for celiac disease in patients with thyroid disorders.[9] In addition, patients with celiac disease sometimes present with iron deficiency anemia.[10,11] However, Graves' disease, iron deficient anemia, and celiac disease occurring in a single patient has not been reported before; we therefore report the first case of Graves' hyperthyroidism associated with iron-deficiency anemia and celiac disease.

Case Report

A 37-year-old woman with no significant past medical history presented to the endocrinology clinic with a one-year history of palpitations, tachycardia, anxiety, diarrhea, and a 20 pound weight loss. Clinical and biochemical findings were consistent with overt hyperthyroidism. Her TSH was 0.02 mIU/L (reference range 0.4-5.5 mIU/L), her free T_4 was 2.9 ng/dL (reference range 0.8-1.8 ng/dL), her T_3 was 388 ng/dL (reference range 60-181 ng/dL), and her thyroid uptake showed homogenous increased 24-hour uptake at 65%. Thyroid ultrasound showed a diffusely enlarged thyroid with no focal lesion.

The patient was started on methimazole, 10 mg bid, and propranolol, 40mg bid, for symptom control. She developed facial rash after starting methimazole, so it was discontinued after three weeks of treatment. Blood tests showed hemoglobin/hematocrit to be 10.9

Table 1. Results of Laboratory Tests

	At initial presentation	**2 months after starting a gluten-free diet**	**7 months after starting gluten-free diet**	**12 months after gluten-free diet**	**Reference range**
TSH	0.02 mIU/L	0.04 mIU/L	0.04 mIU/L	0.03 mIU/L	0.4-5.5 mIU/L
Free T4	2.9 ng/dL	1.1 ng/dL	1.1 ng/dL	1.4 ng/dL	0.8-1.8 ng/dL
Total T3	388 ng/dL	115 ng/dL			60-181 ng/dL
Free T3			337 ng/dL	412 ng/dL	230-420 pg/dL
Hemoglobin	10.9 g/dL	14.4 g/dL	14.0 g/dL	14.0 g/dL	11.5-15.0 g/dL
Hematocrit	33.3%	41.4%	40.5%	40.1%	34.0-44.0%

g/dl/33.3% with a MCV of 68. Iron studies revealed iron-deficiency anemia. Her iron level was 32 µg/dL (reference range 40-175 µg/dL), transferrin saturation was 8% (reference range15-50%), and total iron-binding capacity (TIBC) was 400 µg/dL (reference range 250-450 µg/dL).

The patient was referred to Gastroenterology Department for a work up for anemia and chronic diarrhea. She was found to have positive anti-gliadin antibodies and positive tissue transglutaminase IgG antibodies that are consistent with celiac disease. Endoscopic small bowel biopsies were suggestive of celiac disease. The patient was then placed on a gluten-free diet, which gradually improved her diarrhea and anemia.

Two months after she started a gluten-free diet, the patient was no longer anemic (hemoglobin/hematocrit was 14.4 g/dl/41.4%), and her symptoms improved. She remained clinically euthyroid, and a blood test showed a TSH level of 0.04 mIU/L, a free T_4 level of 1.1 ng/dL, and a T_3 level of 115 ng/dL. She remained clinically euthyroid except for occasional palpitations which were controlled by Toprol XL, 25 mg daily. Twelve months after adopting a gluten-free diet, she gained 4 lbs and blood tests showed a TSH level of 0.03 mIU/L, a free T_4 level of 1.1 ng/dL, and a free T_3 level of 412 ng/dL. See Table 1 for the summary of her laboratory test results.

Discussion

Celiac disease or gluten sensitive enteropathy is an intolerance of dietary gluten that results in immunologically-mediated inflammatory damage to the small intestinal mucosal. The damage is characterized by inflammation, crypt hyperplasia, and villous atrophy.[1,7,12] Celiac disease patients cannot tolerate gluten. Classic symptoms include diarrhea, flatulence, abdominal pain, and weight loss. However, there is an increased incidence of subclinical or silent celiac disease in recent years.[13,7,14]

An increased prevalence of thyroid dysfunction and anemia has been reported in patients with Celiac disease. Iron-deficiency anemia can be an extra-intestinal marker of subclinical celiac disease.[13] Some authors have recommended that patients with iron-deficiency anemia be routinely evaluated for celiac disease.[10,11]

In addition, authors of previous studies recommend routine screening for celiac disease in patients with autoimmune thyroid disease. In a prospective study of 115 patients with Graves' hyperthyroidism by Ch'ng et al.,[9] the prevalence of celiac disease in patients with Graves' hyperthyroidism was found to be 4.5% as compared with 0.9% in age and sex matched controls.

Graves' disease, iron-deficient anemia, and celiac disease occurring in a single patient has not been reported before. In our case, the diagnosis of Graves' hyperthyroidism was based on elevated free thyroid hormones, suppressed TSH levels, and homogenously increased iodine uptake.

Celiac disease was diagnosed by characteristic histological abnormalities on small bowel biopsy, positive antibodies, and a good response to a gluten-free diet. Iron deficiency anemia was based on low serum iron, a low transferrin saturation of 8%, and high TIBC.

Celiac disease and iron deficiency anemia are clinically important because early treatment of celiac disease may prevent or reverse extra-intestinal manifestations, including osteoporosis, anemia, and fatigue, and may reverse some thyroid abnormalities. In this case, the patient's anemia significantly improved on a gluten-free diet. Her symptoms of hyperthyroidism also improved without antithyroid medication. This suggests that treating celiac disease may have reversed the patient's thyroid abnormalities.

Celiac disease should be considered in patients presenting with iron deficiency and hyperthyroidism. The diagnosis of celiac disease can be made based on a combination of serologic testing and pathology. The gold standard for diagnosing celiac disease is a small bowel biopsy sample by which the extent of the damage can be measured.[7,16]

The effective treatment for celiac disease is withdrawal of gluten from the diet. Withdrawal includes the avoidance of all foods containing wheat, rye, and barley. The withdrawal allows the small bowel mucosa and nutrient absorption to normalize.[7,12] Such dietary modifications may correct refractory anemia and hyperthyroidism. If celiac disease is not effectively treated, both benign and malignant complications may occur, such as malabsorption, osteoporosis, infertility, and lymphoma of celiac disease. These complications, however, can often be avoided by early diagnosis and compliance with a gluten-free diet.[1,7] In our case, the gluten-free diet reversed the iron-deficiency anemia and hyperthyroidism, although there exists the possibility of a spontaneous fluctuation of Graves' disease.

Conclusion

We report a unique case of a patient with hyperthyroidism, iron deficiency anemia, and celiac disease. The patient's thyroid function improved and anemia normalized after a gluten-free diet, without antithyroid medication and iron supplementation. Currently it is not known whether treatment of celiac disease reduces the likelihood of developing autoimmune disorders or changes the natural history of Graves' disease. We suggest screening for celiac disease in patients with both hyperthyroidism and iron-deficiency anemia.

Treating celiac disease by withdrawing gluten may reduce morbidity and improve quality of life in patients with hyperthyroidism, iron deficiency anemia, and celiac disease.

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Primary Hypothyroidism Associated with Hyperprolactinemia and Pituitary Macroadenoma

(Full Text Free)

Dragana Jokic, MD and Xiangbing Wang, MD, PhD

Division of Endocrinology and Metabolism,
Robert Wood Johnson Medical School
University of Medicine and Dentistry
New Brunswick, New Jersey

Corresponding Author: Xiangbing Wang, MD, PhD FACE
Division of Endocrinology, Metabolism & Nutrition
Robert Wood Johnson University Hospital-UMDNJ
MEB 384B, 1 RWJ Place, P.O. Box 19. New Brunswick, NJ 08903
Phone (732) 235-7751 Fax (732) 235-7069 E-mail: wangx9@umdnj.edu

Abstract. **Objective**: Our purpose is report a case of primary hypothyroidism associated with hyperprolactinemia and pituitary macroadenoma. **Background**: We present the case report, including detailed laboratory and radiological findings in 28 year old woman. In primary hypothyroidism there is hyperplasia of both thyrotrophs and lactotrophs as a response to TRH hypersecretion. The hyperplasia can result in significant enlargement of the pituitary gland and can be mistaken for a prolactin-secreting tumor. **Case**: We report the case of a female patient who presented with amenorrhea of 7-months duration and was found by her gynecologist to have elevated prolactin. The initial MRI showed a 1.7 cm pituitary mass which was treated initially by cabergoline. Due to the patients noncompliance and lack of follow up, the patient remained on cabergoline for 6 months and did not do thyroid function tests. Finally, after 6 months, a follow up MRI showed no change in size of her pituitary mass. Also, blood tests showed profound hypothyroidism, and after 6 month of thyroid replacement therapy, the patient was euthyroid. A repeated MRI of the brain showed complete resolution of the pituitary mass. Result: This case emphasizes the importance of evaluation of thyroid function in cases of elevated prolactin and gonadal dysfunction. Despite a lack of the typical clinical presentation of hypothyroidism, resolution of the patient's symptoms and disappearance of her pituitary macroadenoma confirms the diagnosis. **Conclusion**: This case illustrates that primary hypothyroidism can present with amenorrhea and pituitary mass.

Keywords • Amenorrhea • Hyperprolactinemia • Hypothyroidism • Pituitary macroadenoma • Prolactin

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Case Reports

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Dragana Jokic, MD and Xiangbing Wang, MD, PhD

Division of Endocrinology and Metabolism,
Robert Wood Johnson Medical School
University of Medicine and Dentistry
New Brunswick, New Jersey

Corresponding Author: Xiangbing Wang, MD, PhD, FACE
Division of Endocrinology, Metabolism & Nutrition
Robert Wood Johnson University Hospital-UMDNJ
MEB 384B, 1 RWJ Place, P.O. Box 19. New Brunswick, NJ 08903
Phone (732) 235-7751 Fax (732) 235-7069 E-mail: wangx9@umdnj.edu

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***Abstract*. Objective**: Our purpose is to report a case of primary hypothyroidism associated with hyperprolactinemia and pituitary macroadenoma. **Background**: We present the case report, including detailed laboratory and radiological findings in a 28-year-old woman. In primary hypothyroidism there is hyperplasia of both thyrotrophs and lactotrophs as a response to TRH hypersecretion. The hyperplasia can result in significant enlargement of the pituitary gland and can be mistaken for a prolactin-secreting tumor. **Case**: We report the case of a female patient who presented with amenorrhea of 7-months duration and was found by her gynecologist to have elevated prolactin. The initial MRI showed a 1.7 cm pituitary mass which was treated initially by cabergoline. Due to the patient's noncompliance and lack of follow up, the patient remained on cabergoline for 6 months and did not do thyroid function tests. Finally, after 6 months, a follow up MRI showed no change in size of her pituitary mass. Also, blood tests showed profound hypothyroidism, and after 6 month of thyroid replacement therapy, the patient was euthyroid. A repeated MRI of the brain showed complete resolution of the pituitary mass. **Result**: This case emphasizes the importance of evaluation of thyroid function in cases of elevated prolactin and gonadal dysfunction. Despite a lack of the typical clinical presentation of hypothyroidism, resolution of the patient's symptoms and disappearance of her pituitary macroadenoma confirms the diagnosis. **Conclusion**: This case illustrates that primary hypothyroidism can present with amenorrhea and pituitary mass.

Keywords ● Amenorrhea ● Hyperprolactinemia ● Hypothyroidism ● Pituitary macroadenoma ● Prolactin

Introduction

Prolactin is a pituitary-derived hormone that plays a pivotal role in a variety of reproductive functions. Prolactin negatively modulates the secretion of pituitary hormones responsible for gonadal function, including luteinizing hormone and follicle-stimulating hormone. An excess of prolactin, or hyperprolactinemia, is a commonly encountered clinical condition and is most commonly secreted in excess by pituitary adenoma. The patient usually presents with galactorrhea and gonadal dysfunction.

It is important to measure prolactin levels in all patients with unexplained primary or secondary amenorrhea. This was emphasized in some previous studies that showed that as many as 20% of patients with hyperprolactinemia did not have galactorrhea nor any signs of pituitary dysfunction. Vilar et al. reported on 1234 patients with different etiologies of hyperprolactinemia, as well as the response of 388 patients with prolactinomas to dopamine agonists.[1]

Vilar et al. found that 56.2% of patients had prolactinomas, 14.5% had drug-induced hyperprolactinemia, 9.3% had macroprolactinemia, 6.6% had nonfunctioning pituitary adenomas, 6.3% had primary hypothyroidism, 3.6% had idiopathic hyperprolactinemia, and 3.2% had acromegaly.[1]

In men, the diagnosis of prolactin-secreting tumors is usually delayed until visual impairment or hypopituitarism appears. The reason is the male's initial signs of gonadal dysfunction. These signs, decreased libido and occasionally galactorrhea, are associated with prolactin excess are usually ignored.

There are many conditions associated with hyperprolactinemia. The most common causes are pregnancy, hypotalamo-pituitary disorders, drugs, and primary hypothyroidism.

With the development of the third generation TSH assay and the inclusion of thyroid function testing in annual blood screenings, hyperprolactinemia caused by primary hypothyroidism become less common. Primary hypothyroidism can be associated with diffuse pituitary enlargement, which reverses with appropriate thyroid hormone replacement therapy.[2,3] However, primary hypothyroidism associated with a pituitary adenoma is extremely rare. Here, we report one such case.

Case Presentation

A 28-year-old female presented at her gynecologist's office with 7 months of amenorrhea in 2009. The patient initially complained also of occasional dizziness, but she did not have headaches, visual disturbances, or galactorrhea. The patient also denied diarrhea or constipation, as well as dry skin, hot and cold intolerance, weight change, and muscle cramps. She never had menstrual abnormalities prior to this episode. She had recently married. Her only medical history was knee surgery 10 years before. Her family history was positive for thyroid cancer, which her sister had. She never smoked or abused alcohol and was exercising regularly.

The initial laboratory work done by her gynecologist was negative for pregnancy, but it showed a prolactin level of 139 ng/mL. An MRI of the brain showed a 1.7 cm pituitary macro adenoma. The adenoma extended into the suprasellar region with indentation of the optic chiasm. Thyroid studies were also ordered but the patient did not follow up for reevaluation.

The gynecologist started the patient on 0.25 mg of cabergoline twice weekly. After 6 months, the patient came back with the same complaint of amenorrhea and a new symptom of "feeling cold all the time." Her prolactin level had decreased to 11.7 ng/mL and an MRI of the brain showed no change in the size of the pituitary adenoma. The patient was referred to an endocrinologist for possible surgery because of failure of the adenoma to shrink. Although no symptoms suggested hypothyroidism except cold intolerance, blood tests showed a TSH of 562.5 µU/mL, a FT_4 of 0.18 ng/dL, and a reference range IGF-1 level. Cabergoline was discontinued and the patient was started on levothyroxine. The dosage was titrated to 112 µg daily.

The patient was closely followed afterwards and 6 months later, her prolactin level was 23.2 ng/mL and her periods were regular; TSH had decreased to 0.237 µU/mL, her total T_3 was 127 ng/dL, and her FT_4 was 1.63 ng/dL. An MRI one year after she had started levothyroxine showed complete resolution of the pituitary adenoma.

Discussion

The hyperprolactinemia of hypothyroidism is related to several mechanisms. In response to the hypothyroid state, a compensatory increase in the discharge of TRH results in an increased stimulation of pituitary prolactin secretion. Hypothalamic thyrotropin releasing hormone (TRH) is a potent prolactin releasing factor, and it can cause thyrotroph hyperplasia.

The high level of TRH in severe primary hypothyroidism and the lack of T_4 feedback from the thyroid gland might cause proliferation and hypertrophy of both the pituitary gland's thyrotrophs and lactotrophs. The hypertrophy may mimic a pituitary adenoma. With proliferation of the thyrotrophs and lactotrophs in primary hypothyroidism, as illustrated in our case, there is a significant increase in TSH levels and only a moderate increase in the prolactin level.

In our patient, regression of her pituitary macroadenoma after treatment with levothyroxine confirmed the hypothesis of pituitary hyperplasia secondary to primary hypothyroidism. Cabergoline decreased her prolactin levels, but it did not decrease the size of the adenoma. This observation also supports the diagnosis of pituitary macroadenoma that was likely secondary to hypothyroidism.

Furthermore, prolactin elimination from the systemic circulation is reduced in severe hypothyroidism; this contributes to increased circulating prolactin concentrations. Primary hypothyroidism can be associated with diffuse pituitary enlargement, which will reverse with appropriate thyroid hormone replacement therapy.

In our case, primary hypothyroidism was not investigated and treated at the beginning of her care

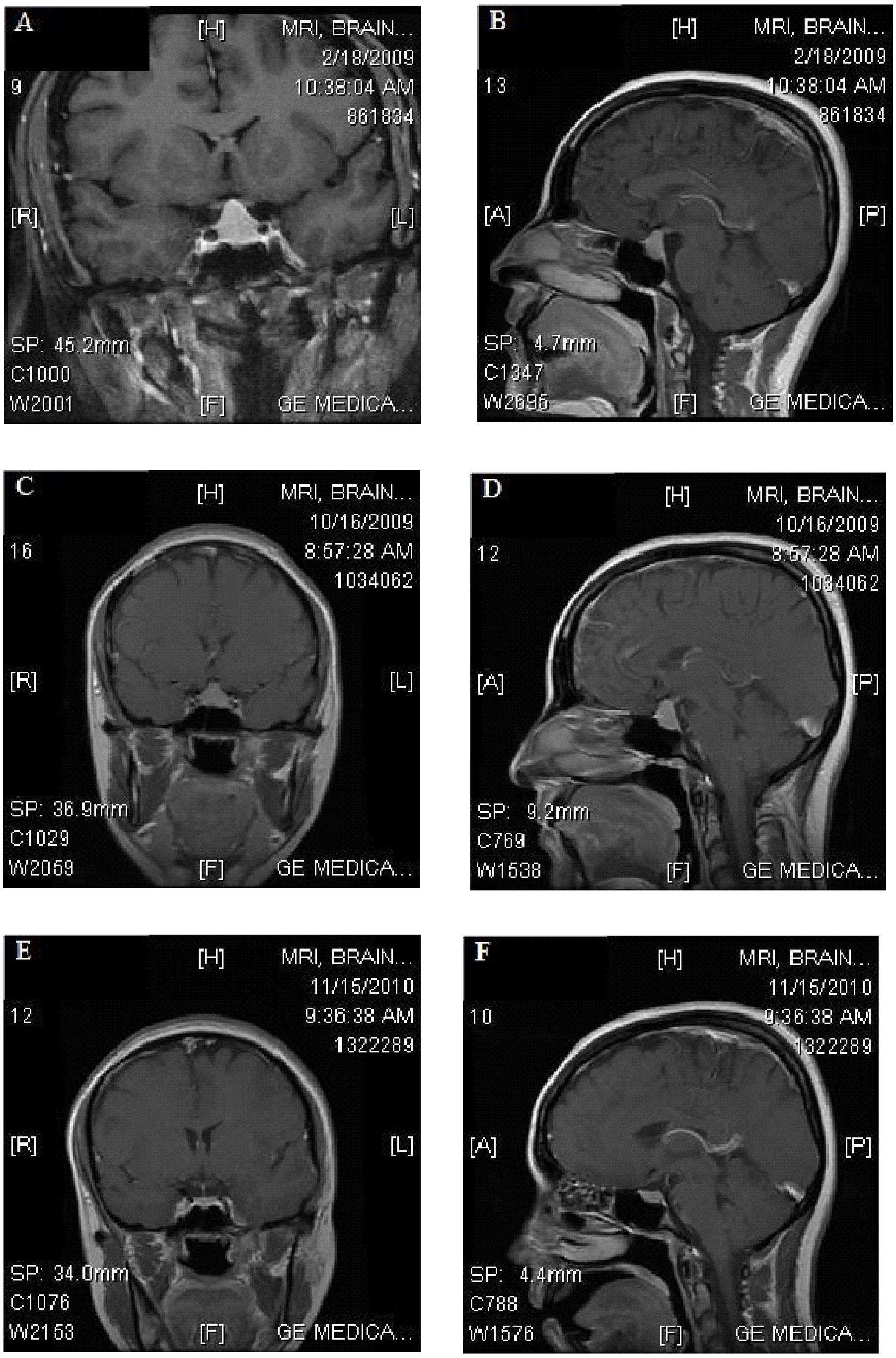

Figure. A and B: Coronal and sagittal post-gadolinium images show a 1.7 cm pituitary macroadenoma extending into the suprasellar region with indentation of the optic chiasm.
C and D: Coronal and sagittal post-gadolinium images show no difference in size of pituitary macroadenoma after 6 months of therapy with cabergoline
E and F: Coronal and sagital post-gadolinium images show complete resolution of the pituitary mass after 6 months of thyroid hormone replacement therapy.

for three reasons: (1) the patient was relatively asymptomatic, (2) presented with a pituitary macroadenoma rather than a diffuse enlargement, and (3) was noncompliant.

This case illustrates the importance of doing thyroid function tests in patients with hyperprolactinemia and pituitary macro adenoma. Doing so can avoid unnecessary pituitary surgery. However, surgical resection of a pituitary adenoma in primary hypothyroidism might still be necessary. In rare cases, for example, paradoxical pressure symptoms and development of a visual field defect will occur in the first months of thyroid replacement therapy. These symptoms suggest that monitoring for pressure symptoms during the treatment is important.[9]

TSH secreting pituitary tumors caused by primary hypothyroidism should be distinguished from true thyrotroph neoplasia that results in secondary hyperthyroidism. The appropriate therapeutic approach is completely different. TSH-omas are usually invasive macroadenomas and are known to be difficult to treat.[6]

The timeline of growth and regression of pituitary adenomas in hypothyroidism after replacement therapy has been started has not been clearly established. Studies show that discontinuation of T_4 replacement in preparation for ^{131}I therapy for only 3 weeks can cause significant enlargement of the pituitary gland.[2] In one reported case, the patient had rapid regression of a pituitary adenoma after one week of T_4 replacement.[7] In our case, the exact time course could not be established. However, regression of the pituitary macroadenoma after treatment with levothyroxine confirmed the hypothesis of pituitary hyperplasia secondary to primary hypothyroidism.

Conclusion

Patients with hypothyroidism do not always present with typical symptoms. Our case illustrates that primary hypothyroidism can present in amenorrhea and pituitary mass. This suggests the importance of thyroid function testing during the investigation of hyperprolactinemia and pituitary adenoma in order to avoid unnecessary surgery.

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Thyroglossal Duct-Cyst

Thyroglossal duct-cyst.

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Papillary Carcinoma in a Thyroglossal Duct Cyst: A Case Report, Review of Literature, and Diagnostic Pitfalls in Fine Needle Aspiration Cytology

(Full Text Free in pdf format)

Narayani Joshi, MD[1] and B.P. Nag, MD[2]

[1]Mahatma Gandhi Medical College & Hospital Jaipur, Department of Pathology
[2]Mahatma Gandhi Medical College & Hospital Jaipur

Correspondencing Author: Dr. B.P.Nag
D-174, Vineet Marg, Bapu Nagar, Jaipur (Rajasthan) 302015
Phone no.: 09828087246 E-mail: drbpnag@gmail.com

Abstract. The incidence of papillary carcinoma arising in a thyroglossal duct cyst is rare and occurs less than 1% of thyroglossal cysts. We report a case of cystic swelling in the mid-line neck in a young female patient. Fine needle aspiration of the cyst revealed colloid material and macrophages CT scan showed a cystic lesion with calcification. Histopathological examination of the cyst showed papillary carcinoma of the thyroid gland.

Keywords • Papillary carcinoma • Thyroglossal duct cyst • Psammoma bodies

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Papillary Carcinoma in a Thyroglossal Duct Cyst: A Case Report, Review of Literature, and Diagnostic Pitfalls in Fine Needle Aspiration Cytology

Narayani Joshi, MD[1] and B.P. Nag, MD[2]

[1]Mahatma Gandhi Medical College & Hospital Jaipur, Department of Pathology,
[2]Mahatma Gandhi Medical College & Hospital Jaipur

**Corresponding Author*: Dr. B.P.Nag
D-174, Vineet Marg, Bapu Nagar, Jaipur (Rajasthan) 302015
Phone no.: 09828087246 E-mail: drbpnag@gmail.com

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Abstract. The incidence of papillary carcinoma arising in a thyroglossal duct cyst is rare and occurs less than 1% of thyroglossal cysts. We report a case of cystic swelling in the mid-line neck in a young female patient. Fine needle aspiration of the cyst revealed colloid material and macrophages CT scan showed a cystic lesion with calcification. Histopathological examination of the cyst showed papillary carcinoma of the thyroid gland.

Keywords ● Papillary carcinoma ● Thyroglossal duct cyst ● Psammoma bodies

Introduction

Thyroglossal duct cysts are the most common non-odontogenic (tooth-forming) cysts in the neck.[1] The cysts are a congenital anomaly that arises from remnants of the thyroglossal duct. It is estimated that 7% of the adult population have these remnants.[2]

The cysts are usually asymptomatic and presentation of the patient with carcinoma is indistinguishable from the benign common thyroglossal duct cyst.[3] Papillary carcinoma occurs in less than 1% of patients. In majority of patients, histological features of papillary carcinoma of the thyroid tissue are demonstrated.[4] Approximately 150 cases of papillary carcinoma arising in thyroglossal duct cysts have been documented in the English language literature.[5]

Case Report

A 20-year-old female patient who was asymptomatic presented to the Department of ENT, Mahatma Gandhi Medical College and Hospital. The patient had midline neck swelling for 1.5 years. On examination, the swelling was 2 x 2 x 1.5 cm in size, cystic, and moved with deglutination and on protrusion of her tongue. She had no history of pain, and she had no associated cervical lymphadenopathy.

Fine needle aspiration cytology was done. The smear revealed colloid material and a few macrophages (Figure 1). Indirect laryngoscope was done and both vocal cords were found to be normal.

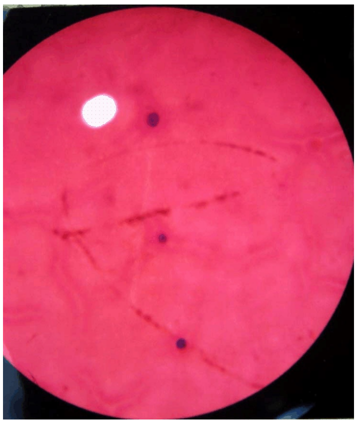

Figure 1. Cytosmear showing macrophages and colloid in the background.

Thyroid function laboratory tests and other biochemical and hematological parameters were within their reference ranges. Ultrasonography showed a septate cyst of 3 x 3 cm in size in the submandibular region. The cyst extended up to the upper pole of the right lobe of the thyroid gland and reached to midline. Both lobes of the thyroid gland were normal in size and echotexture. CT scan revealed cystic swelling of 3 x 3 cm in size on the right side and

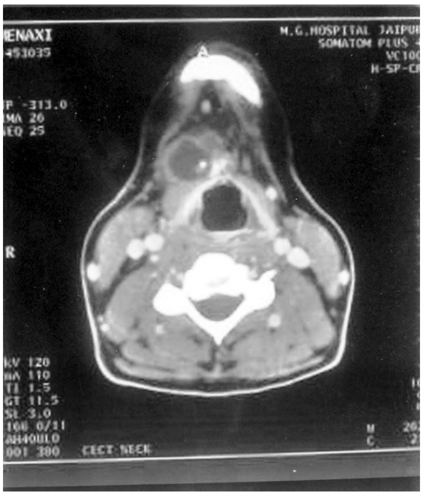

Figure 2. CT scan showing cystic lesion with irregular calcification.

anterior to the right lobe of the thyroid gland with foci of calcification (Figure 2).

The patient underwent excision of the cyst by Sistrunk operation.[6] The cyst was adherent to the hyoid bone. The resected specimen was sent to the department of pathology. On gross examination, the cyst measured 2 x 2 x 1.5 cm in size and was attached to a piece of hyoid bone. On cutting, a roughened internal surface of the cyst wall was seen. Microscopic examination revealed malignant cells arranged in a papillary structure with a central fibrovascular core with multiple calcifications (Psammoma bodies) (Figure 3). The malignant cells displayed optically clear nuclei and some of the cells contained intranuclear inclusions (Figure 4).

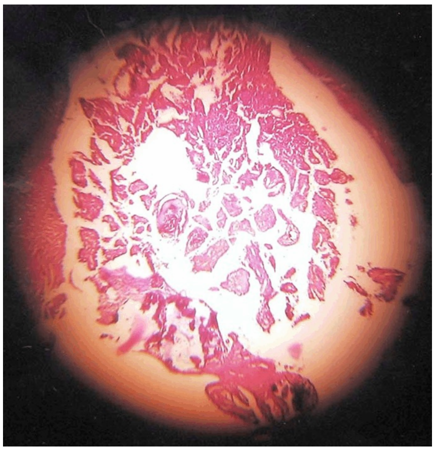

Figure 3. Malignant cells arranged in papillary structure with central fibrovascular core. HE 4 x 10 = 40.

Discussion

Carcinoma of the thyroglossal duct cyst is rare. The clinical presentation is identical to that of a benign cyst.[1] The first case was reported by Uchermann in 1915.[7] The cysts occur most commonly in young women. Geok et al reported a case of papillary carcinoma of the thyroglossal duct cyst in a 15 yrs old girl.[8] Yang also reported papillary carcinoma in thyroglossal cysts in younger women with a sex ratio of 1.5:1.[9] In the present case, FNAC was done. Cytosmear showed only macrophages and colloid material. The false negative result on fine needle aspiration cytology (FNAC) was due to cystic fluid that was aspirated leading to hypocellularity. Godara et al reported on fine needle aspiration the features of colloid goiter with no evidence of malignancy in thyroglossal duct cyst carcinoma.[10] Only fifteen cases of papillary carcinoma in thyroglossal duct cysts diagnosed by FNAC has been reported. Agarwal et al.[11] discussed the diagnostic pitfall of FNAC of papillary carcinoma arising in thyroglossal duct cyst.

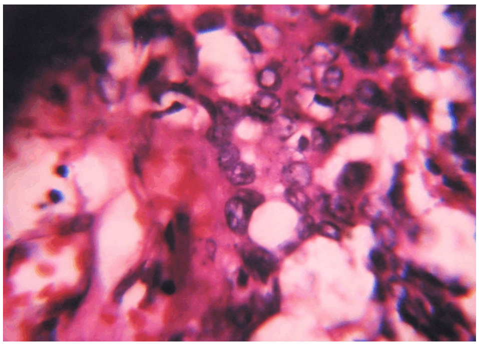

Figure. 4. Malignant cells display optically clear nuclei, some of the central.

Ultrasonography of the cyst revealed a cystic mass with normal thyroid tissue. Smiti reported ultrasonography of the neck showing a well-defined cystic mass in the left paramedian region at the level of hyoid bone with calcification and a normal thyroid gland.[12] CT scan done in our case showed a cyst of 3 x 3 cm in size septate with multiple foci of calcification similar to the findings reported by Taori et al. They reported a midline multi cystic lesion with foci of irregular calcification, a normal thyroid gland, and absence of involvement of neck lymph nodes.[13]

The most common histological pattern demonstrated in patients is that of papillary carcinoma of the thyroid gland, similar to the histological findings described in our case. A case of papillary carcinoma in the thyroglossal cyst without carcinoma in the thyroid gland has also been reported by Yavu et al.[14]

Papillary carcinoma in the thyroglossal duct cyst has a good prognosis and metastasis is reported to be exceedingly rare.[9]

Conclusion

We conclude that papillary carcinoma should be suspected when there are imagine features such as calcification in a midline cystic mass with a normal thyroid gland. This case is reported in view of its rarity and highlights the diagnostic pitfalls of fine needle aspiration cytology.

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Thyroid Science 4(10):CR1-8, 2009

Comparative Effects of Cynomel and Hypo Support Formula

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Dr. John C. Lowe

Director of Research: Fibromyalgia Research Foundation

Correspondence: Dr. John C. Lowe:
drlowe@FibromyalgiaResearch.org, drlowe@drlowe.com
drlowe@FibromyalgiaResearch.org, drlowe@drlowe.com
603-391-6061

Apology

This abstract introduces a study report about a dietary desiccated thyroid product called "HSF." I have written a short editorial apology about two points in the report: (1) a possible error in the report concerning HSF being "organic," and (2) a claim about HSF that in my opinion is false, that is, that it is "thyroxine-free." Some retailers are currently using the report to promote sales of HSF. Because of that, we have corrected the possible error in this reports. Editorial apology.

Abstract. In a previous study, two subjects on stable dosages of the synthetic T3 product Cynomel found dosages of an dietary desiccated thyroid product (Hypo Support Formula or HSF) that maintained or improved clinical measurements provided by the previous dosages of Cynomel. The equivalence of HSF to Cynomel in maintaining the measurements was calculated to be 1 capsule of HSF to 15 mcg of Cynomel. In this study, another subject stable on Cynomel switched to the dosage of HSF previously calculated to effectively maintain the clinical and physiological measurements. **Methods:** A single-subject two-phase repeated-measures study design was used. The subject was a 24-year-old female. She had been stable for a year and a half on 100 mcg of Cynomel. She underwent 12 comprehensive metabolic evaluations on different days in the Cynomel phase. She then immediately switched from Cynomel to HSF and underwent 12 additional evaluations. The evaluations included four basal measures: metabolic rate (BMR), heart rate (BHR), axillary temperature (BAT), and blood pressure (BBP). Other measures were body composition, mean hypothyroid symptoms intensity, Zung's depression scale, and pain distribution. **Results:** The subject's physiological and clinical measurements, stable for 1.5 years on 100 mcg of Cynomel, were not statistically different when she used 7 capsules of HSF each day. The only significant differences in the subject's measures were an increase in pain intensity and distribution during the HSF phase. **Conclusion:** For most measurements, including the BMR, BHR, and BAT, and hypothyroid symptoms intensity including depression, 7 capsules of HSF maintained the same values as 100 mcg of Cynomel. This outcome is consistent with that of the first study in which Cynomel and HSF were compared.

Keywords. Basal metabolic rate • Basal temperature • Cynomel • Desiccated thyroid • Hypo Support Formula • RLC Labs • Triiodothyronine

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Case Reports

Comparative Effects of Cynomel and Hypo Support Formula

John C. Lowe†

†Director of Research: Fibromyalgia Research Foundation
Correspondence: Dr. John C. Lowe: drlowe@FibromyalgiaResearch.org drlowe@drlowe.com, 603-391-6061

Abstract. In a previous study, two subjects on stable dosages of the synthetic T_3 product Cynomel found dosages of an organic dietary desiccated thyroid product (Hypo Support Formula or HSF) that maintained or improved clinical measurements provided by the previous dosages of Cynomel. The equivalence of HSF to Cynomel in maintaining the measurements was calculated to be 1 capsule of HSF to 15 mcg of Cynomel. In this study, another subject stable on Cynomel switched to the dosage of HSF previously calculated to effectively maintain the clinical and physiological measurements. **Methods:** A single-subject two-phase repeated-measures study design was used. The subject was a 24-year-old female. She had been stable for a year and a half on 100 mcg of Cynomel. She underwent 12 comprehensive metabolic evaluations on different days in the Cynomel phase. She then immediately switched from Cynomel to HSF and underwent 12 additional evaluations. The evaluations included four basal measures: metabolic rate (BMR), heart rate (BHR), axillary temperature (BAT), and blood pressure (BBP). Other measures were body composition, mean hypothyroid symptoms intensity, Zung's depression scale, and pain distribution. **Result:** The subject's physiological and clinical measurements, stable for 1.5 years on 100 mcg of Cynomel, were not statistically different when she used 7 capsules of HSF each day. The only significant differences in the subject's measures were an increase in pain intensity and distribution during the HSF phase. **Conclusion:** For most measurements, including the BMR, BHR, and BAT, and hypothyroid symptoms intensity including depression, 7 capsules of HSF maintained the same values as 100 mcg of Cynomel. This outcome is consistent with that of the first study in which Cynomel and HSF were compared.

Key Words. Basal metabolic rate ● Basal temperature ● Cynomel ● Desiccated thyroid ● Hypo Support Formula ● RLC Labs ● Triiodothyronine

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Introduction

Despite the widespread use of dietary desiccated thyroid products, only one product has thus far been tested in a systematic clinical trial.[1] In the study reported here, that product, Hypo Support Formula[2] (HSF), was again tested. The purpose was to determine whether the equivalence of HSF to Cynomel,[3] calculated from data in the first study, would enable a patient stable on Cynomel to maintain the same clinical and physiological status upon switching to HSF.

Methods

Subject. One female subject took part in the study. She was a 24-year-old female. Before starting thyroid hormone treatment with Cynomel in 2006, she was euthyroid according to her TSH and thyroid hormone levels. Despite her biochemically euthyroid status, ten days after beginning the use of Cynomel, she had complete relief of an eight-year history of almost constant profuse bleeding. Her bleeding had been misdiagnosed as Von Willebrand's bleeding disease with a factor VII platelet defect.

Since the age of 14, the subject had suffered from profuse bleeding that had required infusions and medications intended to reduce or stop the bleeding. She had copious, prolonged menstrual bleeding, nose bleeds, bleeding gums, easy bruising of the skin, and severe bleeding during dental procedures. None of the prescribed medications had been more than mildly and transiently effective at reducing her bleeding.

On June 18, 2006, the author measured the subject's basal metabolic rate with indirect calorimetry. Her measured BMR was 620 kcal/day. Using her sex, age, height, and weight in the Mifflin-St.Joer equation, her predicted BMR was calculated to be 1208.74 kcal/day. By this equation, then, her BMR was 48.74% below the predicted rate. By the Harris-Benedict equation, which also uses sex, age, height, and weight, her BMR was 52.25% below the predicted rate. Using her lean body weight of 78.28 lbs (measured with 4-electrode bioelectrical impedance) in the Sterling-Pasmore equation, her BMR was 42.62% below her predicted BMR.

The only likely BMR-lowering factor affecting the subject was inadequate thyroid hormone regulation. This was obvious from a deductive differential diagnosis: she did not have low lean body weight or an androgen deficiency. She also was not restricting her calorie intake, which could severely lower the BMR.[22]

At the time, a substantial research literature existed showing that what was often diagnosed as Von Willebrand's bleeding disease was actually excessive bleeding secondary to hypothyroidism.[25] However, the young woman who is the subject of this study constitutes one of the untold tragedies resulting from the pseudoscientific and dogmatic belief that an elevated TSH is definitive and essential for the diagnosis of inadequate thyroid hormone regulation. Her many well-intending clinicians' harbored the false belief that her reference range TSH levels ruled out a need for thyroid hormone therapy. This false belief was the culprit that subjected the young woman to eight years of dreadful suffering, compromise, and debilitation from chronic, uncontrollable, massive bleeding.

Numerous hematologists, gynecologists, and other specialists included TSH levels in the patient's laboratory testing. But each of these clinicians dismissed the likelihood that inadequate thyroid hormone regulation could be the cause of her bleeding. Their reason was that her TSH levels were within the current reference range. This study subject is a sterling example of the *gross failure* of the TSH to well serve humanity. I reiterate, "Despite her biochemically euthyroid status, ten days after beginning the use of Cynomel, she had full and lasting relief from an eight-year history of almost constant copious bleeding."

On June 13, 2007, when the subject was 23-years-old, she underwent her second BMR. At the time, she was taking 75 mcg of Cynomel. Her BMR was 864 kcal/day. Her lean body weight of 78.6 lbs was high enough so that her predicted BMR (using the Sterling-Pasmore equation) was 1084.68 kcal/day. Her measured BMR, then, was 20.4% lower than her BMR predicted by her lean body weight. Before she had begun to use the 75 mcg of Cynomel, however, her BMR had been 42.62% below her predicted BMR. The 75 mcg of Cynomel, then, had increased her BMR by 22.22%. Because her BMR and other measures indicated that she was still underregulated by thyroid hormone, she increased her daily dose of Cynomel to 100 mcg.

The subject's third BMR measurement occurred on November 19, 2007. She was in her first trimester of pregnancy. Her measured BMR was 1550 kcal/day. Her predicted BMR based on her lean body weight was 1161.96 kcal/day (using the Sterling-Pasmore equation). This BMR was 33.4% above the BMR predicted by her lean body weight. Using the Harris-Benedict equation, the BMR of 1350.85 kcal/day was 14.74% above the predicted BMR; and using the Mifflin-St.Joer equation, her BMR of 1275.66 kcal/day was 21.51% above the predicted BMR for her sex, age, height, and weight.

Predictably, opponents of the use of any thyroid hormone preparation other than levothyroxine (T_4) will hastily attribute the patient's increased BMR to overstimulation by her use of Cytomel. However, her increased BMR is entirely consistent with the increased basal energy expenditure of pregnancy.[51,52] That 100 mcg of Cynomel did *not* account for her increased BMR is shown by her reference range BMRs after her pregnancy while still using 100 mcg of Cynomel.

For example, the author performed another comprehensive metabolic evaluation for the subject on May 24, 2008. The reader should bear in mind that in calculating a "normal" BMR for patients, a "reasonable" reference range is considered to be 10% below or above the calculated average. On May 24, 2008, the subject's BMR of 1200 kcal/day was 4.8% above the BMR calculated from her lean body weight, and, using two different equations for sex, age, height, and weight, her measured BMR was 1.5% and 8% below the calculated average. All three equations indicate that her Cynomel dose of 100 mcg per day provided her with a "normal" BMR.

Procedures. Upon waking from sleep and when comfortable with the temperature and bedding, the subject measured her basal metabolic rate with a hand-held indirect calorimeter (the Med Gem®, Healthetech, Golden, Colorado). She then measured her basal temperature of her left armpit with an electronic thermometer that gave a digital reading (Walgreens model VT-820W5T). In another study by the author,[7] this type of electronic thermometer was compared to measurements with Galinstan-in-glass thermometers (Geratherm Medical AG, Fahrenheitstraße 1, D-98716 Geschwenda), which are equivalent to mercury thermometers. Measurements with the electronic and Galinstan thermometers strongly correlated and were highly consistent.[7] After taking her basal axillary temperature, the subject then took her basal pulse rate and blood pressure with an electronic sphygmomanometer (Omron Healthcare, Inc., Model HEM-711ACN, Bannockburn, IL).

After arising from bed, the subject drank two 8-ounce glasses of water, and, after urinating, measured her height and weight on a balance beam scale (Healthometer, Continental Scale Corp., Bridgeview, IL). She then measured her body composition by 4-electrode bioelectrical impedance (Biodynamics® Model 310, Seattle, WA).

Next the subject filled out three sets of evaluation forms: (1) a questionnaire with visual analog scales for 12 major symptoms characteristic of hypothyroidism;[6] (2) Zung's Self-rating Depression Scale (W.W.K. Zung © 1991); and (3) body drawings with 36 divisions for shading in the distribution of pain since the previous evaluation.[11]

After each evaluation, all measurements and scores were tabulated in an Excel spreadsheet in preparation for statistical analyses.

Study Design. An intrasubject replication study design (also termed a two-phase single-subject repeated measures design) was used.[8-16] Statistical comparisons were made of the data from the first, the Cynomel phase, and the second, the HSF phase.

In the Cynomel phase, the subject underwent 12 clinical evaluations. These occurred between October 10 and December 21, 2008. In the HSF phase, she underwent an additional 12 clinical evaluations. These occurred between December 26, 2008 and March 21, 2009. The mornings that the subject chose to undergo evaluations were selected on two bases: convenience, and the perception that she was, upon awakening, in a mental and physical basal state.

Before the study began, the subject had been stable on a daily dose of 100 mcg of Cynomel.[3] She continued Cynomel at that dosage until she had completed 12 clinical evaluations. The morning after she completed the 12th evaluation, she ceased taking Cynomel and began taking HSF. Her HSF dosage was calculated from the physiological equivalence derived from the first comparative study of Cynomel and HSF.[1] The equivalence was 1 capsule of HSF for each 15 mcg of Cynomel. She therefore immediately began taking a daily dose of 7 capsules of HSF. The 7 capsules were equivalent to 105 mcg of Cynomel, but based on experience in previous clinical trials by the author with synthetic T_3,[44,45,47,48,49] the additional 5 mcg were considered clinically insignificant.

During each of the phases, the subject underwent several electrocardiograms (ECGs). The tracings were compared with ECGs performed before the study began in case adverse cardiac effect began to develop.

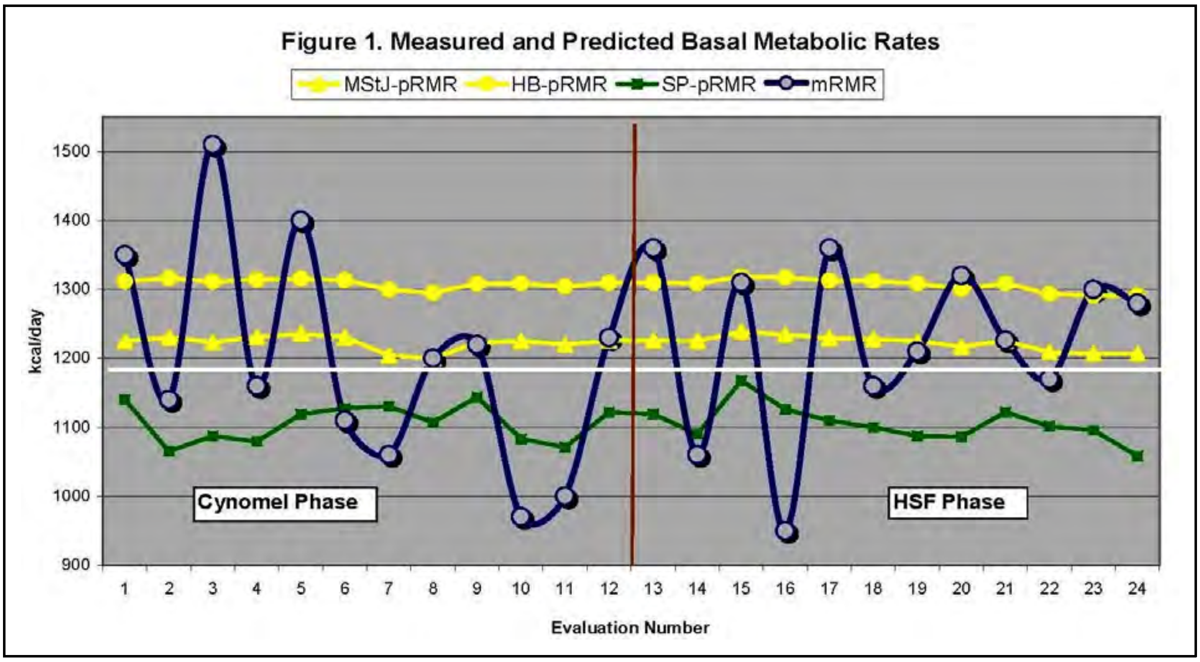
When the study began, the subject filled out a sheet of visual analog scales containing common symptoms of thyrotoxicosis. The scores on the sheets were compared to subsequent sheets during and after the study as indicators of possible symptoms of thyrotoxicosis.

Statistical Analyses. The *t*-test was used to test for differences between mean measurements. Levene's test for equality of variances was used to test for differences in the variance of measurements between the Cynomel and HSF phases. Bloom's probability table was used to statistically analyze any differences between Cynomel and HSF phases by the trend line method. The level of significance was set at $p \leq 0.05$. Statistical analyses were performed with SPSS for Windows® (SPSS, Inc., Chicago, IL), VassarStats: Website for Statistical Computation, and Microsoft® Excel 2002.

Results

Basal Metabolic Rate. The subject's mean measured BMR during the Cynomel phase did not significantly differ statistically from that in the HSF phase (1195.83 ± 161.10 kcal/day vs 1225.50 ± 124.93, $p = 0.619$). Variances of the BMRs within each phase also did not differ ($F = 0.548$, $p = 0.467$).

Figure 1 contains the subject's measured BMRs. Each BMR along the blue trend line is represented by an empty circle. By Bloom's probability table,[5] with the baseline including 12 BMRs (left side of graph), and 6 below and 6 above the trend line (see the white horizontal line), 10 measured BMRs in the HSF phase (right half of graph) would have to be above or below the trend line for HSF-phase BMRs to be significantly different from those in the Cynomel phase. This criterion is not met. The lack of a significant difference using this method is consistent



with the lack of difference in the mean measured BMRs of the two phases determined through the use of the *t*-test.

Basal Axillary Temperatures. In the Cynomel phase of this study, shown in the left side of the graph in Figure 2, two temperature measurements (the 3rd and 4th) appear very low compared to the other measurements. The two measurements were 95.18°F (35.10 °C) and 94.82°F (34.90°C). However, these two measurements did not fall outside two 2 standard deviations from the mean. The mean was 96.66°F (35.92°C), and two standard deviations below the mean was 94.75°F (34.86°C). Because the two low measurements were within two standard deviations from the mean, they were included in the statistical calculations. The mean axillary temperature during the Cynomel phase (96.66°F [35.92°C]) did not significantly differ from that in the HSF phase (96.91°F [36.06°C]). The variances of the temperature readings in the two phases also did not differ.

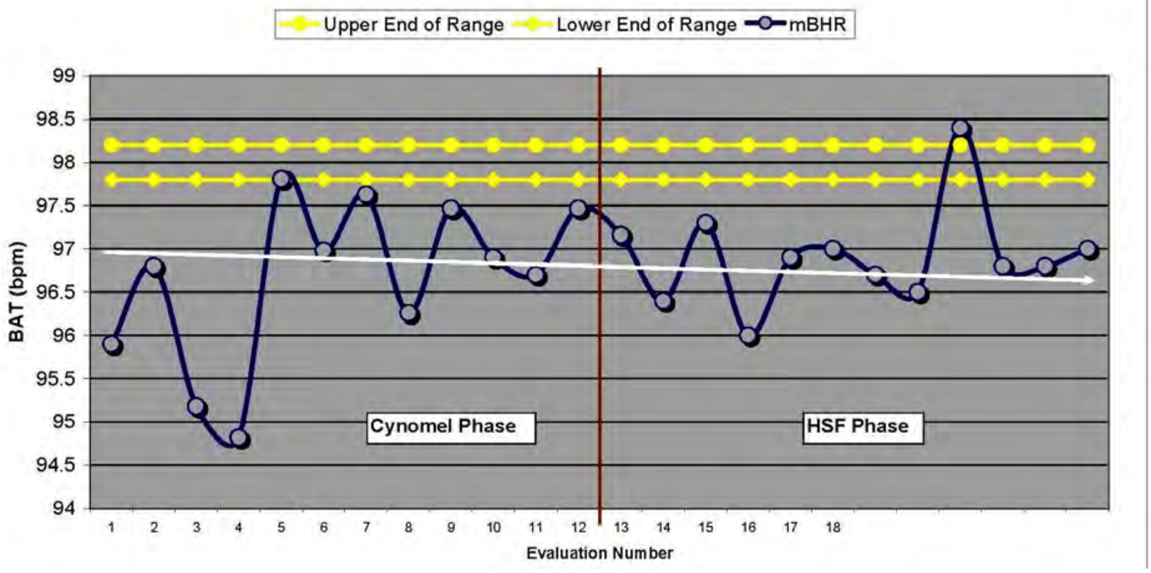
The result of using the probability table of Bloom[5] is consistent with the results of use of the *t*-test for the means of the two groups of temperatures. Bloom's table also shows no significant difference. With 12 measurements in the Cynomel phase (left half of graph), with 6 data points above the trend line and 6 below (see the white line in Figure 2), 10 data points above or below the trend line in the HSF phase (right half of the graph) would be necessary for a significant difference between the two phases. This criterion is not met.

Basal Heart Rates. The subject's mean basal heart rate in the Cynomel phase did not significantly differ from that in the HSF phase (79.50 ± 9.15 vs 81.50 ± 4.78 bpm, $p = 0.51$). However, the variances of the two sets of heart rate measurements did differ (F= 5.42 $p = 0.03$). The *large* difference in the variability of the subject's heart rate is visibly obvious in the graph in Figure 3. Her heart rate varied far more in the Cynomel phase than in the HSF phase. The standard deviation of the rate in the Cynomel phase was 9.15 and in the HSF phase was 4.78.

Use of the probability table of Bloom[5] shows no significant difference in the heart rates between the two phases. With 12 heart rate measurements in the Cynomel phase (left half of graph), with 6 above and 6 below the trend line (see the white horizontal line in Figure 3), 10 data points would have to be above or below the trend line in the HSF phase (right half of the graph) for the subject's heart rate to have significantly changed during the HSF phase. This criterion is not met, so the subject's heart rates in the two phases did not significantly differ.

Blood Pressure. The subject's mean systolic pressure and diastolic pressure did not differ between the Cynomel and HSF phases. Variability in the pressures also did not significantly differ

Figure 2. Basal Axillary Temperature (BAT)



between the phases.

Body Composition. No significant differences were found between the Cynomel and HSF phases for fat weight, percent body fat, lean body weight, nor any of three measures body water content.

Mean Symptoms Intensity. The subject's mean hypothyroid symptoms intensity did not significantly differ between the two phases. Variability of the symptom intensities in the two phase also did not significantly differ.

The subject's scores in the two phases on Zung's Self-rating Depression Scale did not significantly differ. The variability of the Zung's scores in the two phase also did not significantly differ.

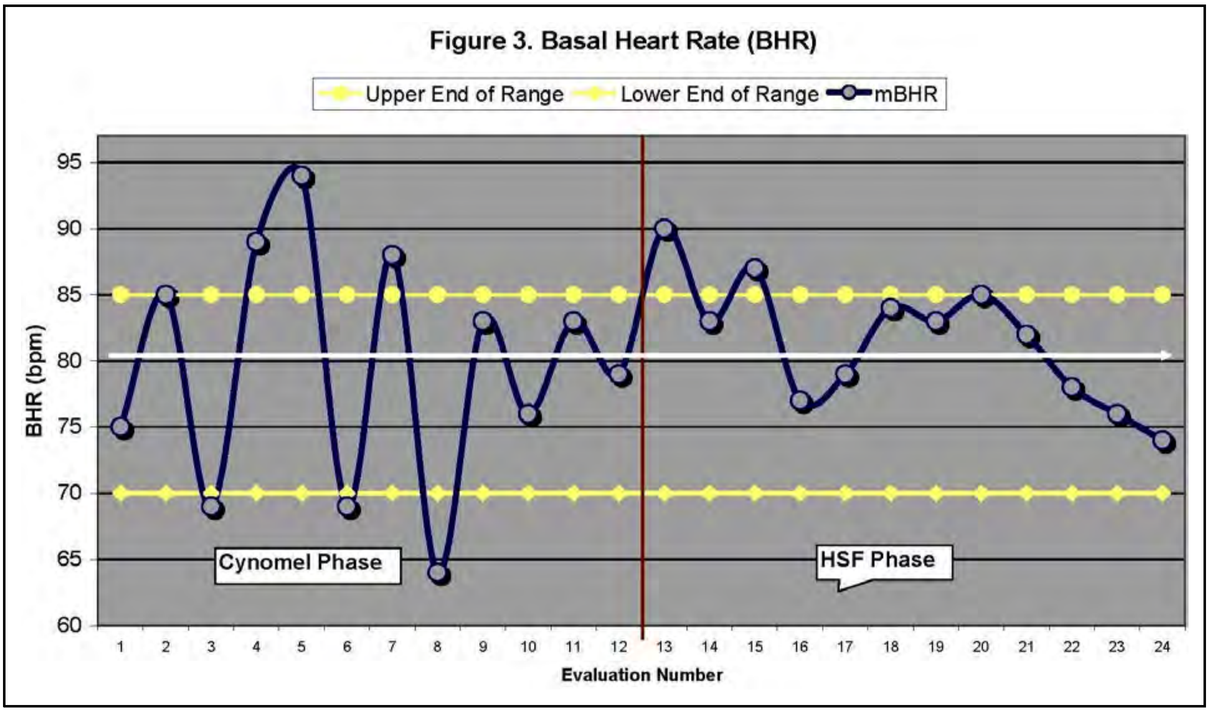
Pain Scores. The patient's estimated pain intensity (1-to-10 point severity scale) was significantly higher in the HSF phase than in the Cynomel phase (6.875 ± 0.99 vs 4.8892 ± 1.50, p = 0.001). Her pain distribution was also significantly higher in the HSF phase than in the Cynomel phase (29.62% ± 7.05 vs 15.25% ± 3.42, p = 0.001). The subject's pain distribution across 36 body divisions significantly and positively correlated with the intensity of her pain (r = 0.68, p = 0.003).

Discussion

The physiological and clinical measures used in this study indicate that HSF was as effective as Cynomel. No symptoms of thyroid hormone overstimulation nor ECG abnormalities occurred during the subject's use of Cynomel or HSF. The only exception is that the subject's pain intensity and distribution were significantly higher during the HSF phase. No significant changes in the subject's body body composition occurred during the study. Although her basal axillary temperatures were below the lower limit of the range established by Barnes, her temperatures did not significantly differ in the two study phases.

Comparative Effects of Cynomel and HSF. In this study, the subject used HSF, a dietary desiccated thyroid product, as a substitute for Cynomel, a synthetic T_3 product. Her use of HSF in a phase that included 12 comprehensive metabolic evaluations followed a phase in which she had also undergone 12 such evaluations while using Cynomel. During the phase in which she substituted 7 capsules of HSF for 100 mcg of Cynomel, her physiological measures did not significantly differ from those in the preceding Cynomel phase. Except for an increase in pain intensity and distribution, her symptoms did not significantly differ in the two phase. The results of this study are consistent with those of the first study of HSF and Cynomel[1] in that 1 capsule of HSF appears to be physiologically equivalent to 15 mcg of Cynomel.

Safety. In neither of the two phases of the study did the subject develop symptoms of thyrotoxicosis.



This was partly determined by comparing the intensity ratings of symptoms of thyrotoxicosis on visual analog scales that the subject filled out before the study and at intervals during the two phases.

The subject was not hyperreflexic. Her Achilles reflex speed was normal in both the contraction and relaxation phases.

Before the subject study began and during each phase, the subject underwent several electrocardiograms (ECGs). Tracings made during the study were compared with those before the study began. The tracings before and during each phase of the study were essentially the same, showing no indication of altered electrical rate or rhythm.

The lack of thyrotoxicity, normal Achilles reflexes, and unchanged normal ECGs indicate that neither Cynomel nor HSF in the dosages the subject used had adverse effects.

Pain. The subject's pain intensity and pain distribution were both significantly higher in the HSF phase than in the Cynomel phase. She has for extended times used each product alone. Her subjective impression is that when using Cynomel, she has less joint pain, which is a lifelong symptom of hers. She also believes she sleeps better when using Cynomel. Improved sleep could account for her lower pain scores during the Cynomel phase.[26,27,28]

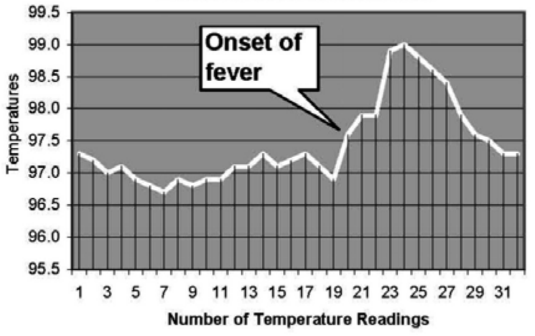
The subject's increased pain perception and pain scores on HSF is different from findings in the first study comparing HSF and Cynomel.[1] In that study, both the male and female subjects had subjective improvement in pain perception. Only the male subject, however, had statistically significant reductions of his scores for pain intensity and distribution. (For a discussion of possible factors involved in pain and thyroid hormone regulation, please see the discussion section of the previous study report.[1])

Body Composition. No significant differences were found in any measures of body composition between the Cynomel and HSF phases. No changes were found in fat weight, percent body fat, lean body weight, nor any measure of body water content. The subject's impression, however, is that she has retained less weight when using Cynomel than when using HSF. Lower weight when using Cynomel, however, was not objectively confirmed in this study. While her weight was lower in the Cynomel phase than in the HSF phase (107.29 ± 1.157 vs 106.39 ± 2.213 lbs), the difference was not statistically significant ($p = 0.229$).

Basal Axillary Temperatures. The subject was stable on 100 mcg of Cynomel before this study. She remained completely free from the chronic, profuse bleeding that had dominated her life for 8 years. She also had BMRs that were close to those predicted from her lean body weight and her sex, age, height, and weight, and on one occasion, a BMR consistent with the increased energy expenditure of pregnancy.

Despite these benefits, the patient's basal axillary temperatures were typically below the lower end of the reference range reported by Barnes (97.8°F-to-98.2°F).[4] For example, the mean of 19 basal axillary temperatures that she took between August 20, 2007 and September 7, 2007 was 97.03°F (36.13°C). In the two phases of this study, however, her basal temperatures were, respectively, 96.66°F (35.92°C) and 96.91°F (36.06°C).

Figure 4. Subject's Basal Axillary Temps: Aug.20,2007-Sept.20, 2007. Fever between 20th and 31st Measurements



Regardless of these low temperatures, the subject was capable of increased temperatures during infections. Figure 4 shows her basal axillary temperatures between August 20 and September 20, 2007. During the later half of that span of time, she contracted an infection. She felt feverish, had malaise and swollen cervical lymph nodes, and she was bedridden for the better part of a week. Her 20th measurement, taken when her symptoms had begun, showed an increased basal temperature. Her temperature ascended and by the 31st measurement had declined considerably back toward her lower mean temperature.

Limitations. This study was unblinded and this raises the possibility of observer bias. The number of repeated measurements, however, and the objective nature of the methods of measurement make it highly unlikely that the outcome was influenced by subtle biases.

The single-subject two-phase repeated measures design used in this study has merits lacking in randomized studies. The subject in this type of study, for example, serves as his or her own control in the two different phases. This eliminates the need for randomization, as the subject in each phase is as perfectly matched as possible to the subject in the other phase. Moreover, repeated measures under systematically varied conditions provides data for both traditional group statistical analyses and clear visual inspection for functional relationships between independent and dependent variables.

Conclusion

The results of this study show equivalent effects of HSF and Cynomel on all physiological measurements used and on most clinical assessments tools. The results are therefore similar to those of the first study[1] that assessed the effects of the two products.

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T3-Induced Recovery from Fibromyalgia by a Hypothyroid Patient Resistant to T4 and Desiccated Thyroid*

(Full Text Free in pdf format)

Dr. John C. Lowe

Director of Research,
Fibromyalgia Research Foundation

Correspondence: Dr. John C. Lowe
drlowe@FibromyalgiaResearch.com, drlowe@drlowe.com
Tel: 603-391-6060 Fax: 303-496-6200
FibromyalgiaResearch.org, drlowe.com

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Abstract to Case Report

The case report we present here was originally published in 1995. The case study was not blinded, but it was *highly* systematic. Three clinicians (a neuropsychiatrist; a physical therapist; and myself, a chiropractic physician) working in our separate clinical practices in different locations, evaluated the patient using objective measures. The data that I presented in the report of this case report fifteen years ago, and again now, was collected by the three independent clinicians each of whom worked simultaneously with the patient.

This systematic single case shows three noteworthy features of the patient: First, she was hypothyroid; second, she met the American College of Rheumatology criteria for fibromyalgia; and third, she no longer met those criteria and fully recovered when we switched her to T3 therapy after T4 and desiccated thyroid had failed to benefit her. It is worth emphasizing that the patient continued to meet the criteria for fibromyalgia when being treated with T4 (Synthroid) and then with desiccated thyroid (Armour). However, she quickly and dramatically recovered—no longer meeting the criteria for fibromyalgia—when we switched her treatment to plain T3 (Cytomel) with her daily dose well within the physiologic range.

I asked that *Thyroid Science* republish this case report for two reasons: First, many people have requested reprints of the original case report. To get reprints, these patients and clinicians had to contact my office. The reason is that the paper is no longer available online or in an accessible journal. In 1996, McDowell Publishing Company, LLC, who owned the journal that first published the report, sold the journal to Haworth Medical Press. The latter publisher, however, did not make available the journal issue that the case report had been published in. *Thyroid Science*'s open-access republishing of the paper now makes it perpetually available to anyone who finds its contents of interest.

My second reason for asking that *Thyroid Science* republish the report is the utter failure of fibromyalgia researchers in general to open their eyes to an obvious truth: that inadequate thyroid hormone regulation is the main underlying mechanisms of most patients so-called fibromyalgia. That I say that this is an obvious truth does not mean that all cases of fibromyalgia are easily solved simply by treating treating the patient with the proper form and dosage of thyroid hormone. As my colleague David Derry, MD, long ago pointed out in the British Journal of Medicine, living long years with untreated or undertreated hypothyroidism causes most patients to accrue secondary, tertiary, and other health complications that also must be disentangled from the enlarging clinical knot that further encumbers the patients. That a patient's fibromyaliga is long-standing usually means that successful recovery is a more complicated process.

Nonetheless, deductively formulated theory (the mathematical physicist's tool of victory that is absent from the intellectual armamentarium of the fibromyalgia establishment) shows unequivocally that the main underlying mechanism of fibromyalgia is too little thyroid hormone regulation. The inadequate thyroid hypothesis accounts for virtually *all* objective evidence we have on fibromyalgia. In stark contrast, no other hypothesis accounts for more than a minute fraction. Ignoring this fact forsakes fibromyalgia patients the world over, but it brings in a king's ransom from the purchase of ineffective and potentially harmful "fibromyalgia drugs" such as Lyrica and Cymbalta.

Why do fibromyalgia researchers in general ignore the obvious? Through more than two decades of involvement in this field, I have learned a list of disreputable reasons: prejudice against the possibility of a causative thyroid connection, ignorance of basic and clinical thyroidology, egotistical pursuit of failed pet theories, and corruption through acceptance of judgment-forming grants and other perks from Big Pharma to develop drugs for fibromyalgia that are palliative at best and harmful at worst.

Despite many prominent fibromyalgia researchers claiming to be pursuing the underlying mechanism(s) of what we call fibromyalgia, they look everywhere but in the right direction. But while the researchers have spent decades looking in all the wrong directions, countless fibromyalgia patients—such as the female I describe in the case report—have recovered full health by the intelligent use of thyroid hormone as part of a comprehensive program of metabolic rehabilitation. Many have accomplished this by taking their health care into their own hands, while others have had the help of enlightened and collaborative clinicians.

My friend and colleague Richard L. Garrison, MD, for example, with T3 therapy and other assertive thyroid therapies, helped countless fibromyalgia patients to recover their health. This infuriated jealous physicians who had gaven the patients quack diagnoses of psychiatric disorders. Dr. Garrison was brutally punished for his crime of being scientific, humanitarian, and effective with patients. But emails I still receive some 3 years after his death tell me that for every physician who detested his clinical successes with fibromyalgia patients is at least matched by recovered patients who still adore him for enabling them to recover their health.

I republish this 1995 report with sorrow in my heart over the persecution of courageous physicians such as Dr. Richard L. Garrison who relieved so many patients suffering with the intelligent use of thyroid hormone. My sorrow is even deeper, however, over the millions of fibromyalgia patients who today are improperly treated for profit with Big Pharma's drugs. As my colleagues and I showed many years ago (and typified by the case we republish today in *Thyroid Science)*, the continued suffering of most of those people is avoidable. But sadly, we now live in a world where drug companies and researchers they fund steadily more make their fortunes from sustaining the suffering of other human beings.

I find it more than difficult at times to live with the awareness that millions of fibromyalgia patients spend their lives suffering needlessly. But I find some solace in a famous statement by physicist Max Planck, the founder of quantum theory: *"A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it."*

And happily, a new generation appears to me to be sprouting in the field of fibromyalgia. At this time, Ian R. Carroll, MD at Stanford University School of Medicine is conducting a study of T3 for fibromyalgia patients. The title of his study is, "T3 for Fibromyalgia: a Pilot Double-blind Non-randomized Clinical Trial." I have no idea yet how this study will unfold. No research team I am aware other than mine has extensive research and clinical experience in treating fibromyalgia patients effectively with T3. But Dr. Carroll was unaware of my research team and our work until recently, when I learned of his study and sent him a copy of my book *The Metabolic Treatment of Fibromyalgia.* As his pilot study nears its end, he and I have just begun to correspond.

With no intent of malice, but only the hope of seeing the relief of untold and unnecessary human suffering, I am impatient for the passing of that generation of closed-minded fibromyalgia researchers. Before much more time passes, I hope to see a new and enlightened generation of researchers and clinicians that declines to assign the label "fibromyalgia" to people with chronic widespread pain and simply treats them effectively for their hypothyroidism or thyroid hormone resistance. In the mean time, if the case we republish today leads to even one patient's pain relief tomorrow, I will pleased indeed that I wrote the report fifteen years ago.

Max Planck, PhD
Circa 1947

John C Lowe

Original Abstract. The main purpose of this case report is to illustrate a clinical observation common to me: that fibromyalgia patients with central hypothyroidism who fail to benefit from T4 or desiccated thyroid completely recover when they switch to T3. Changing status in the patient was evaluated in three ways: a psychiatrist used a depression inventory, a physical therapist performed functional musculoskeletal assessments, and I performed algometer tender point exams and monitored symptoms. I hope the description of the management of this case provides a protocol that other clinicians will use with fibromyalgia patients similar to the one who is the subject of this report.

Key Words. Algometry • Desiccated thyroid • Fibromyalgia • Hypothyroidism • T3 • T4 • TSH

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Case Reports

T_3-Induced Recovery from Fibromyalgia by a Hypothyroid Patient Resistant to T_4 and Desiccated Thyroid*

Dr. John C. Lowe

Director of Research,
Fibromyalgia Research Foundation

Correspondence: Dr. John C. Lowe
drlowe@FibromyalgiaResearch.com, drlowe@drlowe.com
Tel:603-391-6060 Fax: 303-496-6200

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Abstract. The main purpose of this case report is to illustrate a clinical observation common to me: that fibromyalgia patients with central hypothyroidism who fail to benefit from T_4 or desiccated thyroid completely recover when they switch to T_3. Changing status in the patient was evaluated in three ways: a psychiatrist used a depression inventory, a physical therapist performed functional musculoskeletal assessments, and I performed algometer tender point exams and monitored symptoms. I hope the description of the management of this case provides a protocol that other clinicians will use with fibromyalgia patients similar to the one who is the subject of this report.

Keywords • Fibromyalgia • Hyperthyroidism • T_3 • T_4 • TSH • Desiccated thyroid • Algometry

Introduction

A number of researchers in the 1950s and 1960s reported that hypothyroid patients responded to T_3, the metabolically active thyroid hormone, after failing to benefit from T_4, desiccated thyroid, or thyroglobulin.[8][9,p.13][10,p.274][11][12][13][14] Many of the symptoms the patients in these reports recovered from are remarkably similar to those characteristic of fibromyalgia. The symptoms are listed in Table 1.

The fibromyalgia patient whose case I report here resembles the patients in the 1950s and 1960s case reports in two respects: first, she shares with them the same general symptoms; and second, she responded to T_3 afer failing to benefit from desiccated thyroid. The patient discussed in this report and other fibromyalgia patients may be modern day examples of those 1950s and 1960s patients.

Like fibromyalgia patients studied by Ferraccioli and coworkers[18] and Neeck and Riedel,[19] this patient had a blunted TSH response to TRH, and this, combined with her thyroid hormone profiles, indicates that she had central (probably pituitary) hypothyroidism. Her complete recovery from fibromyalgia may point the way to relief for other fibromyalgia patients with central hypothyroidism.

METHODS

Patient. The patient in this case study was a 41-year old Caucasian female. She was a homemaker and mother of two children.

On March 2, 1993 the patient's automobile, traveling at 20 miles per hour, struck another that came into her path. Immediately after the impact, she experienced neck and left shoulder pain. Subsequently, she underwent treatment, seriatim, by a chiropractic physician, a medical physician, a physical therapist, two additional chiropractic physicians, and myself. I concurred with the other practitioners that the patient had a traumatically-induced regional cervical injury but also diagnosed her as having fibromyalgia. Apparently she had had fibromyalgia symptoms for many years.

At the beginning of the study, she indicated on body drawings that she had widespread pain according to the American College of Rheumatology 1990 criteria:[23] pain above and below the waist and on the left and right sides of her body. The body areas she shaded on the drawings included the anterior, posterior, and

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lateral neck, the upper posterior thoracic area, the supraspinatus muscles, the interscapular region down to about the T6 spinal level, and the low back and gluteal muscles. She described her pain as "throbbing, aching, burning, and sometimes shooting and stabbing." she stated that her muscles felt too tense. She also reported the symptoms listed in Table 2.

Previous Treatment. On March 25, 1988 her psychiatrist prescribed desiccated thyroid. The supplement was intended to increase her energy level and serve as an adjunct to the antidepressant Desyrel. She also took the antidepressant Wellbutrin. She continued the thyroid supplement until we began this study although it benefitted her only in one way: her coldness decreased in distribution. Before taking desiccated thyroid, her whole body was cold. After beginning the supplement, only her hands and feet were cold—the Raynaud's-like symptom of fibromyalgia.

After delivering a baby in March 1990, she experienced severe post-partum depression and started an estrogen supplement.

Table 1. Six sets of symptoms reportedly relieved by T_3 after T_4, desiccated thyroid, or thyroglobulin failed to relieve them.

1. Aching in both knees, skin pallor, facial puffiness, a dull feeling, and tiredness.[8]
2. Lethargy, easy fatigue, nervousness, irritability, sensitivity to cold, headache, musculoskeletal pain, diminished sexual potency, and menstrual irregularities.[9]
3. Chronic fatigue, muscle and joint aches, excess weight, bowel dysfunction, cold intolerance.[10]
4. Muscle aches, stiffness, chronic fatigue, excess weight, menstrual disturbances, dry hair and skin, brittle fingernails, nervousness, irritability, depression, mental apathy, puffiness of the face.[11]
5. In school children, poor school records, short attention span, lack of ability to concentrate, "don't care attitude," anxiety, restlessness, poor appetite, constipation.[12]
6. Muscle and joint pains, fatigue, irritability and mood swings, lethargy, decreased libido, premenstrual tension, GI disturbances, scalp seborrhea or hair loss, palpitations, and shortness of breath.[13]

Methods of Assessment. There were several forms of evaluation.

Musculoskeletal functional evaluation. A physical therapist performed functional musculoskeletal assessments of the patient on three occasions.

Psychiatric evaluation. The patient filled out a Zung's Self-rating Depression Inventory on July 23, 1994 at the beginning of treatment and on January 13, 1995 at the end.

Fibromyalgia evaluation. The patient's fibromyalgia status was assessed through three methods: weekly pain drawings, mean algometer scores (the average of the pressure/pain thresholds of the 18 tender points), and diaries of symptoms. Between July 2 and August 8, 1994, I performed five baseline algometer exams. Between August 14, 1994 and January 27, 1995, I performed 19 treatment-phase algometer exams.

Laboratory evaluation. The patient's laboratory profiles were available dating back to 1988. Each included a CBC, SMAC, lipid profile, and thyroid profile. At my request, on July 6, 1994, an internist performed a TRH-stimulation test to evaluate the patient's TSH response to TRH, the hypothalamic hormone. Between July 19 and 20, 1994, he also performed a dexamethasone suppression test to assess adrenal cortical function.

In the TRH-stimulation test, the internist drew a blood sample to establish the patient's TSH serum baseline level. Thirty minutes after injecting TRH, he drew a second blood sample to measure the change in the TSH level. The baseline level was 0.88 IU/ml; the second TSH level was 7.83 IU/ml. This was a blunted TSH response to TRH.

The internist also measured the patient's serum cortisol on July 19, 1994 which was 16.65 ug/dl. After he injected the patient with the synthetic glucocorticoid dexamethasone, he again measured the cortisol level on July 20, 1994. The value was 0.84 ug/dl. This constituted proper adrenocortical suppression.

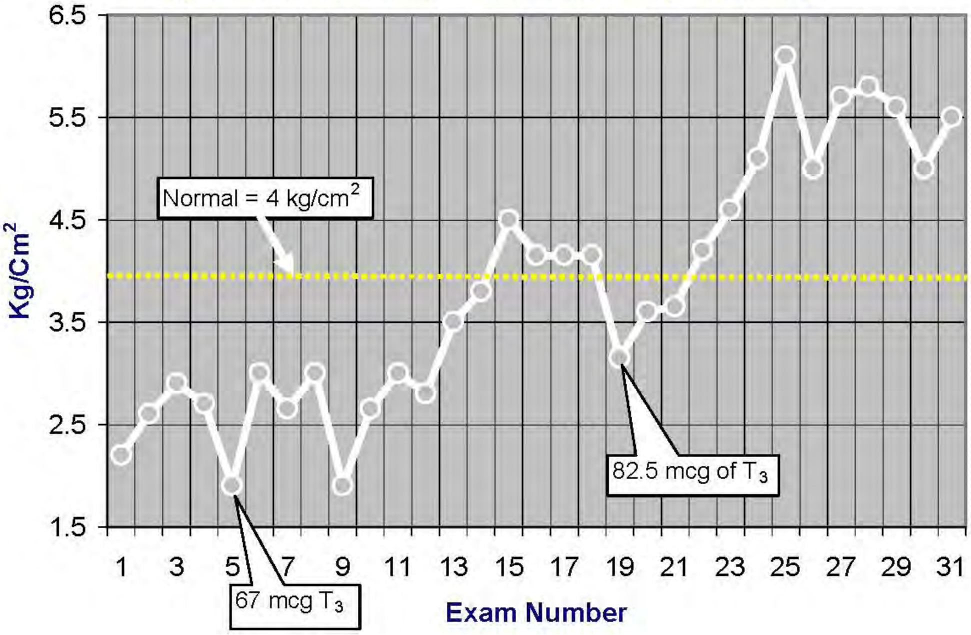
Imaging procedures. The patient had cervical plain film x-rays that were taken on April 7, 1993. She had a cervical MRI on May 26, 1994. In the radiology report, dated May 27, 1994, the radiologist noted that the patient had a "small central disc bulge and small posterior osteophytes at C5-C6." The MRI study was otherwise unremarkable.

Treatment. After her automobile accident on March 2, 1993, the patient had treatment at intervals by two other chiropractors. Each performed directional non-force technique (a gentle manual spinal treatment procedure). She also received treatment several times by a physical therapist. The treatment involved exercise therapy and manual cervical traction. This treatment continued during the case study.

The patient took Armour desiccated thyroid from 1988 until the beginning of this case study. She was taking 2 grains when she first consulted me. Throughout the treatment phase of the study, she took various doses of T_3 prescribed by her psychiatrist. After the baseline period (the first five exams), she abruptly stopped her desiccated thyroid hormone intake and immediately began taking T_3. Her starting dose was 67 mcg of T_3. On November 15, 1994, she increased her dosage to 82.5 mcg. She did so because of a brief reappearance of her symptoms and a drop in her mean algometer score.

Throughout the study, the patient held constant her intake of Ciba Estraderm patch, containing 4 mg of estradiol. On November 17, 1995 she stopped her previous 100 mg of Wellbutrin. She continued to take Desyrel on occasion. During the study, she received in my office treatment with ultrasound, soft tissue manipulation, moist heat, stretch and spray, and manual cervical traction.

Figure 1. Mean Tender Point Scores by Algometry



RESULTS

Changes in Musculoskeletal Function. The patient's physical therapist performed three functional exams. On April 13, 1994, the therapist wrote: The patient "has two children, ages 4 and 13. She is unable to play games with them because of her symptoms. She has a housekeeper full-time and has not done significant housework, gardened, swum, or exercised since her accident. Sleeping is uncomfortable."

On June 10, 1994, the therapist wrote that the burning sensation in the patient's neck and shoulders had improved 75%. She still had dysfunction and trouble sleeping.

On September 23, 1994, the therapist wrote: The patient "has been seen weekly for chiropractic treatment and began taking T_3. She reports a dramatic improvement in her energy level. Now she has periods when she is pain-free. She states she is able to exercise now up to 1½ hours without feeling extreme fatigue as in the past." The patient's grip strength and shoulder flexor strength had improved bilaterally. She was able to sleep through the night most nights, and she had a marked increase in all ranges of cervical motion. Flexion and retraction were no longer painful. The patient did, however, still have regional pain and cervical spinal dysfunction associated with her cervical traumatic injury.

Changes in Psychiatric Status. On July 23, 1994, the patient's raw score on the Zung's Depression Inventory was 43. This converts to an SDS index of 54. The equivalent clinical global impression for the index is "presence of minimal-to-mild depression." On January 13, 1995, some six months later, her raw score on Zung's was 28. This converts to an SDS index of 35. The equivalent clinical global impression for this index is "within normal range: no psychopathology."

Changes in Fibromyalgia Status. By October 4, 1994–about two months after beginning T_3–the patient no longer met the 1990 criteria for fibromyalgia.[23]

Pain drawings. By September 21, the patient's pain decreased from widespread (according to the ACR 1990[23] criteria). She continued, however, to have regional pain related to her cervical injury.

Algometer scores. On October 4, 1994, the patient's mean algometer score exceeded 4 kg/cm^2, the cut off point for normal.

Figure 1 shows the weekly mean algometer scores graphically plotted to show the change over a six-month period. The horizontal axis shows the number of each weekly measurement, and the vertical axis shows the pressure (applied with an algometer, registered in kg/cm^2) she could tolerate before experiencing discomfort at the tender point sites. When viewing the graph in Figure 1, keep in mind that the patient began taking 67 mcg of T_3 on August 8, 1994. On this date, I performed her 5th algometer exam and recorded the result on the graph. Because her symptoms briefly worsened and her mean algometer score dropped, she increased the dosage to 82.5 mcg on November 11, 1994 (the date of her 20th algometer exam).

Table 2. Symptoms reported by the patient at the beginning of the case study.

1. Sleep disturbance.
2. Prolonged morning stiffness (requiring 2-to-12 hours to loosen).
3. Occasional irritable bowel syndrome.
4. Daily headaches.
5. Depression.
6. Poor memory and concentration.
7. Cold hands and feet.
8. Chronic fatigue and sluggishness.
9. Husky voice.
10. Coarse, rough skin.
11. Puffy face and eyes.
12. Not sufficiently alert and attentive.
13. Difficulty losing weight.
14. Dry hair that fell out easily.

Visual inspection reveals an increase in the patient's mean algometer scores beginning the 13th week of the study. In the 19th week, the scores fell but not to baseline. But within three and a half weeks, they ascended again reaching and exceeding the normal value of 4 kg/cm^2. The scores remained above normal for the rest of the study and throughout follow-up.

Symptoms. At the end of the case study, the patient was completely free from all the symptoms listed in Table 2. Her pain was intermittent and limited to her posterior cervical and left upper thoracic regions.

She reported during several post-study follow-up contacts that her status had continued to improve. At follow-up on April 1, 1995, she maintained that she had remained free from all aspects of fibromyalgia for six months and thus considered herself completely recovered.

Changes in Laboratory Values. Four thyroid panels were available and are listed in Table 3. The profile performed in March 1988 shows that the patient's TSH, T_4 (RIA) and T_3 (RIA) were low normal. In July 1994, this same pattern prevailed, and the TRH-stimulation test performed on the same day shows a blunted TSH response. This indicated that she had central (probably pituitary) hypothyroidism.

The September 1994 and January 1995 profiles show that the TSH level decreased and the T_4 (RIA) decreased. In contrast to the March 1988 profile, however, the T_3 (RIA) increased above normal. This pattern indicates that her supplemental T_3 was inhibiting the pituitary glands's thyrotrophs so that they secreted a lower quantity of TSH. The lower exposure of thyroid gland cells to TSH apparently resulted in a reduced secretion of T_4.

Table 3. Four thyroid panels available on patient.

Date	Test	Value	Reference Range
03-28-88:	T_4 (RIA)	8.0	(5.5-11.5 µg/dL)
	T_3 (RIA)	133.00	(90-200 ng/dL)
	TSH	1.7	(0.4-4.3 µg/dL)
07-06-94:	T_4 (RIA)	6.4	(4.5-12.5 µg/dL)
	T_3 Uptake	25%	25% - 35%
	T_7	1.6	1.0-4.0 Units
	TSH	0.7	(0.4-6.0 µg/dL)
09-07-94:	T_4 (RIA)	1.8	(4.5-10.9 µg/dL)
	T_3 (RIA)	154.00	(60-181 ng/dL)
	TSH	0.89	(0.35-5.5 µg/dL)
01-19-95:	T_4 (RIA)	1.6	(4.5-10.9 µg/dL)
	T_3 (RIA)	199.00	(60-181 ng/dL)
	TSH	0.43	(0.35-5.5 µg/dL)

DISCUSSION

Study Design. The format of this study was a single-subject design, also called a "functional design." Chiropractic and medical researchers currently most value another study design–one that tests hypotheses by comparing the responses of groups of subjects to therapeutic interventions. Such comparisons of groups are excellent for testing hypotheses. But investigators who use functional or single-subject designs are not so much concerned with hypothesis testing. Instead, they are concerned with quantifying a patient's response to a therapeutic intervention and measuring it repeatedly through the course of treatment. It is the *functional relationship* between the two variables (the therapy and the response) that interests them. Behavioral scientists–who typically are far better grounded in logic and the philosophy of science–make an argument that other clinical researchers could (were they to listen) profit from:

meaningful hypotheses seldom if ever derive from studies that compare differences between groups. By contrast, such hypotheses *do* tend to emerge inductively from the data derived from functional or single-subject studies.[24]

Most medical researchers measure groups of subjects' responses once before and once afer the therapy. By contrast, investigators conducting single-subject studies measure the subject's responses repeatedly throughout the course of the study. These repetitive measures provide a more detailed account of changes in the subject's responses over time. They show the *process* of therapeutic change plotted against the amount or intensity of therapeutic stimulus. This can reveal with clarity the functional relationship between the therapy and the patient's responses to it.[4,pp.29-37] We should use a functional design with single subjects when we aim for greater precision than group studies allow in determining the relationship between the independent variable (treatment) and the dependent variable (the patient's measured response).[4,p.14] I posit that the thorough failure of other fibromyalgia researchers to unearth the nature of or effective treatment for fibromyalgia is a direct outgrowth of their naive distrust of clinical observation and single-subject case studies.

Changes in Zung's Depression Inventory. The change in the patient's Zung's Depression Inventory indicates that she experienced a decrease from "minimal-to-mild" depression to "within the range of normal." This might be interpreted as reflecting an increase in serotonin secretion. The increase can be predicted to result from thyroid hormone stimulation decreasing the number of inhibitory á-adrenergic receptors and increasing the number of stimulatory â-adrenergic receptors on her CNS serotonergic cells. This would disinhibit their secretion of serotonin.[25,p.137] Also, increased numbers of â-adrenergic receptors in her CNS due to transcription regulation by T_3-thyroid hormone receptor complex may have increased the metabolism of CNS neuronal pathways that mediate a non-depressed mental state.

Interpretation of Laboratory Tests Results. In the TRH-stimulation test, the internist drew a blood sample to establish the patient's TSH serum baseline level. After injecting TRH, he drew a second sample after 30 minutes. The change from the baseline TSH level of 0.88 IU/ml to the 30-minute post-injection level of 7.83 IU/ml indicated a suppression of TSH response to TRH. There are several possible mechanisms for this blunted TSH response.

Was the patient's T_4 elevated and her TSH low because of her estrogen supplement? The patient used a transdermal estrogen patch. It is not likely that this accounted for her low TSH values. Oral estrogen supplements tend to increase the concentration of thyroid-binding globulin (TBG) in the blood. They do so by increasing sialylation of TBG, prolonging its biologic half-life.[1] This occurs because the liver clears a large percentage of the estrogen during its first passage through the liver, resulting in high liver estrogen concentrations. Even the low-dose estrogens in today's oral contraceptives increase TBG concentrations slightly. Only in occasional patients, however, does the serum total T_4 exceed normal limits.[2,p.336]Transdermal estrogen therapy allows the hormone to enter the circulation gradually rather than in the bursts characteristic of oral estrogen therapy. Because of this, estrogen does not accumulate in high concentrations in the liver. As a result, TBG levels may increase only a little.[3] It is unlikely, then, that suppression of TSH secretion by elevated thyroid hormone levels due to increased TBG levels would account for the patient's suppressed TSH response to TRH.

Was the patient's blunted TSH response due to hyperadrenocortical secretion? During the dexamethasone suppression test, the patient's serum cortisol level decreased from 16.65 ug/dl on July 19, 1994 to 0.84 ug/dl on July 20, 1994 after an injection of the synthetic corticosteroid dexamethasone. This was an adequate suppression of adrenocortical secretion of endogenous cortisol indicating that the patient did not have hypersecretion of endogenous cortisol. From this result, I concluded that the patient's blunted TSH response to TRH was not likely due to suppression of the pituitary thyrotrophs and obstruction of T_4-to-T_3 conversion by excess concentrations of cortisol. The result of this test is also inconsistent with the previous findings of failed adrenocortical suppression in some fibromyalgia patients.[18][20]

Comparative Doses of Desiccated Thyroid and T_3. When various investigators reported benefits from T_3 after patients had failed to improve with desiccated thyroid,[8][9,p.13][10,p.274][11][12][13][14] Jefferies objected that the doses of T_3 were higher than those of desiccated thyroid, and that the higher doses were responsible for the benefits rather than the form of thyroid hormone.[6] This is incompatible with many of my clinical observations. Many patients under Poo's and my care[22] took doses of T_4 and desiccated thyroid high enough to produce distinct thyrotoxicosis. When the patients stopped taking desiccated thyroid and switched to T_3, however, fibromyalgia symptoms dramatically improved or ceased completely without toxicity on doses that were proportionately lower than the thyrotoxic doses of T_4 and desiccated thyroid.

This indicates that in some way, T_3 corrects or overrides the underlying mechanisms of fibromyalgia symptoms when T_4 or desiccated thyroid does not do so. One possible explanation for this difference is that T_4 (in desiccated thyroid and products such as Synthroid and Levothroid) is not effectively converted to T_3, the metabolically active thyroid hormone. If this were true, laboratory tests would show high cortisol output, low TSH, and high reverse T_3. Laboratory profiles I ordered have not shown this pattern in some two hundred of my patients who failed to respond to T_4 or desiccated thyroid but later, after the lab tests, responded to T_3. It is not likely, therefore, that a conversion problem is responsible for this therapeutic outcome.

Patient's Blunted TSH Response to TRH. Neeck and Reidel[19] found that 17 female fibromyalgia patients had a blunted TSH response to injected TRH. My patient also had a blunted TSH response. A blunted TSH response implies a deficiency of TSH, and secondarily, yet without certainty, a thyroid hormone insufficiency. The insufficiency can produce fibromyalgia symptoms.[15] Correcting the thyroid hormone insufficiency can relieve the fibromyalgia symptoms. If the patient's fibromyalgia symptoms were due solely to a thyroid hormone deficiency, conventional medical thought would be that T_4 or desiccated thyroid would relieve the symptoms. My patient, however, failed to respond for some seven years to two grains of desiccated thyroid (equivalent to 0.2 mg of T_4), a considerable dose.

The purpose of this case study was to determine whether my patient would respond to T_3 after failing to respond to T_4. She did, and this suggests that her symptoms were not due solely to a thyroid hormone deficiency. An alternate mechanism for her failure to respond to desiccated thyroid or T_4 is mutated thyroid hormone receptors.[21] It is possible that such mutations require that she take 86 mcg of T_3 to recover from fibromyalgia. T_3 probably was required at the cellular level to relieve her symptoms.

Possible Placebo Response of Patient. After numerous clinicians reported that patients improved on T_3 after failing to benefit from desiccated thyroid or T_4, Jefferies in 1961 argued that T_3 was probably a placebo and referred to the "suggestibility of many patients."[6,p.533] He wrote: "The practicing physician is, of course, often in a poor position from which to exercise critical judgement as to the relative efficacy of drugs in his patient. The patient consults a physician because he wishes to feel better, and the physician treats the patient with a sincere desire to oblige. Hence, the two together unconsciously conspire to produce a result pleasing to both."[6,p.534]

In the way of an answer, one must concede that double-blind studies are nonpareil in clinical science. When data from blinded studies are not available, however, it is clearly unreasonable to ignore other forms of evidence, although they are less rigorously derived than data from blinded studies. The issue brings to mind Carlton Fredericks' response to opponents of orthomolecular therapy.[7,p.97] Calling clinical observations "unblinded" is justified. But calling them "uncontrolled" is logically incorrect. In other published studies mentioned above and in this one, patients improved with T_3 *after they had failed to improve over a period of months or even years with desiccated thyroid or* T_4. Because of this, each patient was her own control. Patients' lack of response to desiccated thyroid and T_4 over a prolonged period provided a baseline against which to plot their degree of response to T_3.

The patient who is the subject of this report took substantial doses of desiccated thyroid for seven years without benefit, but she responded dramatically to T_3. Critics such as Jefferies warn that the response may be a placebo reaction. This is to say that the patient would have responded just as well if tablets contained an inert substance rather than T_3. The obvious reply is: Where was the placebo effect when she was taking desiccated thyroid or T_4? Why does T_3 cause a placebo response when other forms of thyroid hormone fail to do so? The likelihood that T_3 acted in this case report and other reports as a placebo is infinitesimally small.

Studies have shown no other therapies for fibromyalgia to be significantly effective,[16] while millions of fibromyalgia patients suffer non-remitting symptoms.[17] Because of this, clinicians and researchers should not ignore the possible benefits of T_3 therapy for their fibromyalgia patients.

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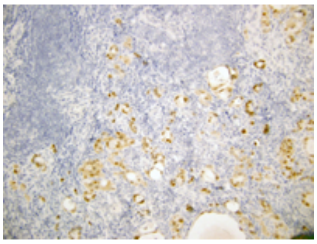

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Struma Ovarii:
Case Report and Review

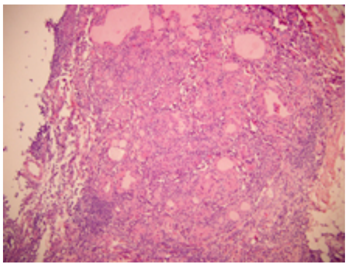
(Full Text Free in pdf format)

Lakshmi Meenakshisundaram, MBBS
and James Bingham, MD

Someset Hospital
225 south center avenue
Somerset, PA 15501

Correspondence: Dr. Lakshmi Meenakshisundaram
Tel: 814-483-4132 pa2ljr@comcast.net

Abstract. Only 150 cases of struma ovarii (i.e., goiter of the ovary) have been reported in the medical literature. The condition is characterized by the presence of thyroid tissue in an ovarian tumor, typically as a part of a teratoma. We report the first case of Hashimoto's thyroiditis concurrent with struma ovarii, a thyroid gland with Hürthle cells, and positive antithyroid antibodies despite reference range thyroid function test results.



Case Report. A young woman presented to the office with pelvic pain. Ultrasound revealed a complex right ovarian mass. The mass was surgically removed, and biopsy revealed struma ovarii with Hashimoto's thyroiditis. After surgery, the patient's thyroid stimulating hormone level decreased into to within the reference range. Her free T4 and free T3 are within their reference ranges, although her thyroid peroxidase and antithyroglobulin levels are elevated. She continues to remain asymptomatic with reference range thyroid function test results. We recommend that physicians maintain a high index of suspicion this struma ovarii in young patients who present with an ovarian mass, as resolution of thyroid function abnormalities can be achieved by surgical removal of the ovarian mass.

Key Words. Hashimoto's thyroiditis • Hürthle cells • Immunohistochemical stain • Struma ovarii • Teratoma

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Case Reports

Struma Ovarii:
Case Report and Review

Lakshmi Meenakshisundaram, MBBS
and James Bingham, MD

Someset Hospital
225 south center avenue
Somerset, PA 15501

Correspondence: Dr. Lakshmi Meenakshisundaram
Tel: 814-483-4132 pa2ljr@comcast.net

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Abstract. Only 150 cases of struma ovarii (i.e., goiter of the ovary) have been reported in the medical literature. The condition is characterized by the presence of thyroid tissue in an ovarian tumor, typically as a part of a teratoma. We report the first case of Hashimoto's thyroiditis concurrent with struma ovarii, a thyroid gland with Hürthle cells, and positive antithyroid antibodies despite reference-range thyroid function test results. **Case Report**. A young woman presented to the office with pelvic pain. Ultrasound revealed a complex right ovarian mass. Her TSH levels was elevated. The mass was surgically removed, and biopsy revealed struma ovarii with Hashimoto's thyroiditis. After surgery, the patient's TSH level decreased into the reference range, and her free T_4 and free T_3 levels remained within their reference ranges. However, her thyroid peroxidase and antithyroglobulin levels are elevated. She continues to remain asymptomatic with reference-range thyroid function test results. We recommend that physicians maintain a high index of suspicion of struma ovarii in young patients who present with an ovarian mass, as resolution of thyroid function abnormalities can be achieved by surgical removal of the ovarian mass.

Keywords Hashimoto's thyroiditis • Hürthle cells • Immunohistochemical stain • Struma ovarii • Teratoma

Introduction

Struma ovarii is a rare entity, with only 150 reported cases in the medical literature. It is characterized by the presence of thyroid tissue in an ovarian tumor, typically as a part of a teratoma.[2]

Struma ovarii was first described by Von Kalden in 1895 and Gottschalk in 1899.[1] Most struma ovarii are benign with only 5%-to-10% being malignant.[3] Hyperthyroidism is seen in about 8% of patients[4] with struma ovarii, but most cases of struma ovarii are asymptomatic from a thyroid standpoint with the majority of patients presenting with symptoms attributable to mass effect, such as pelvic pain.

The pathophysiology has not been clearly defined. Struma ovarii can be identified on histological exam. In difficult cases, immunohistochemical stains for thyroid transcription factor and/or thyroglobulin will confirm the diagnosis of struma ovarii.[5] The diagnosis is usually made after surgical resection of the pelvic tumor. Rarely struma can have characteristics of Hashimoto's thyroiditis. We hereby report a very rare case of struma ovarii presenting with abnormal thyroid function studies due to Hashimoto's thyroiditis.

CASE REPORT

A 48-year-old woman was seen by her gynecologist for mild pelvic pain of insidious onset. Her abdominal and pelvic examinations were noted to be unremarkable. However, pelvic ultrasound showed a complex right ovarian mass. She subsequently underwent a laparoscopic right salpingo-ophorectomy.

The pathology of the surgical specimen revealed a dermoid cyst with a 1 cm tan-white mural nodule. Histological examination of the nodule showed Hürthle cells with abundant pink cytoplasm, nuclear pleomorphism, and prominent nucleoli (Figure 1). The sheets of cells were infiltrated with lymphocytes. Foci of cells forming follicles were identified at the periphery of the nodule.

Immunohistochemical stains revealed the cells to be positive for thyroid transcription factor stain (Figure 2). These findings are consistent with Hashimoto's thyroiditis arising within an ovary, which is designated "struma ovarii." The patient was then referred to our clinic for endocrine evaluation.

Her medical history revealed that she was diagnosed with thyromegaly after the birth of her first child approximately 18 years before. She had been on thyroid hormone therapy for two years until the birth of her second child. At her initial visit, she denied symptoms of thyroid dysfunction and further denied any local neck symptoms referable to her thyroid. She was not aware of any anterior neck/thyroid enlargement at the time of the visit.

However, physical examination her thyroid gland was performed and revealed that the gland was minimally enlarged, firm, and had a bosselated texture consistent with Hashimoto's thyroiditis. Preoperative laboratory testing revealed that her serum thyroid stimulating hormone level was 5.73 uIU/mL (0.35-to-5.5 uIU/mL) with referance-range T_4 and T_3 levels.

Immediately after the surgery, the patient's serum TSH was 3.33 uIU/mL (0.35-to-5.5 uIU/mL) and remained within the reference range at 4-months follow-up. Her antithyroglobulin antibody titer was 851 IU (0-to-24 IU) and her antithyroid peroxidase antibody titer was 1492 IU (0-to-4 IU). A thyroid ultrasound showed a diffusely heterogeneous sonographic appearance, which was interpreted as consistent with Hashimoto's thyroiditis. One year following her ovarian surgery, the patient remains asymptomatic and her serum TSH remains is within the reference range.

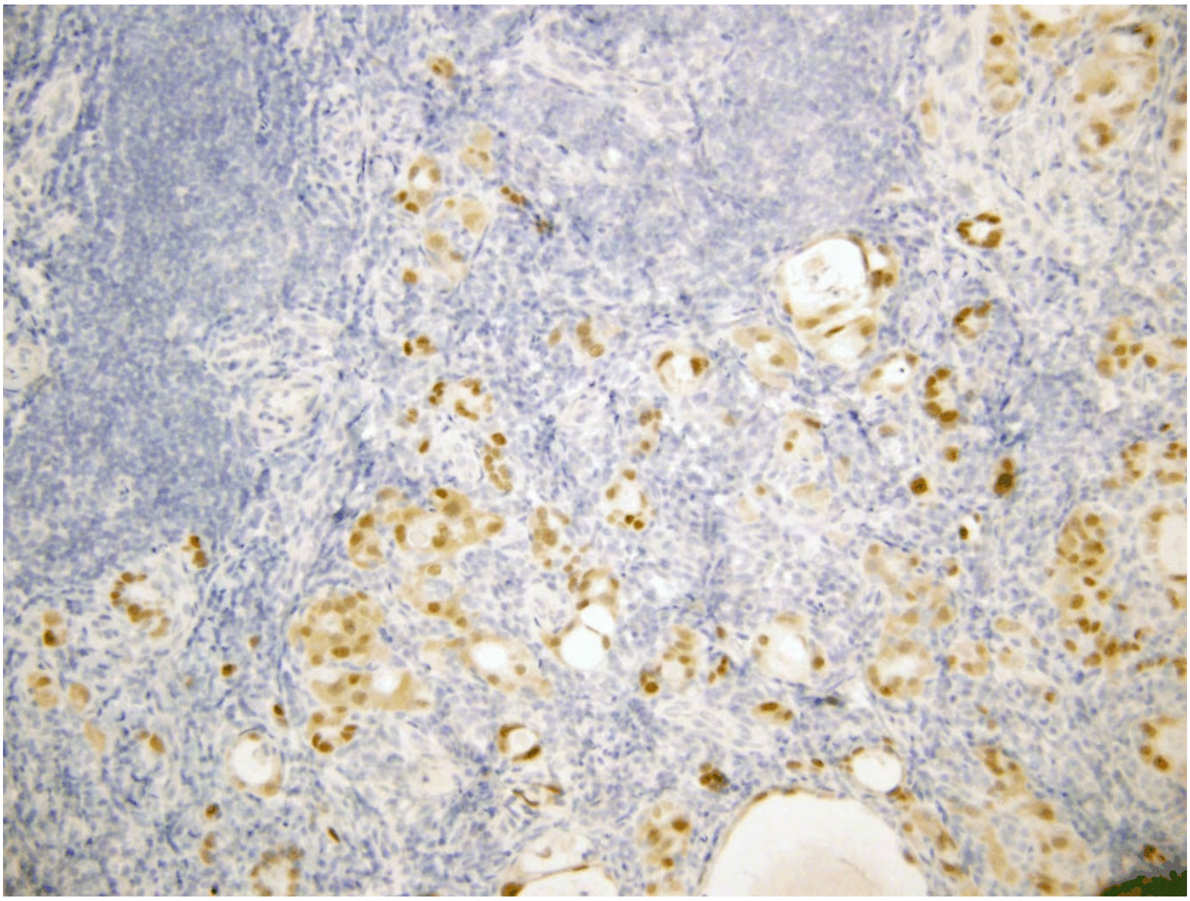

Figure 1. Follicles with Hürthle cell change and infiltrating lymphocytes. Low mag (10x).

DISCUSSION

Struma ovarii with pathologic evidence of autoimmune thyroiditis is uncommon. In 1965, Erez et al.[6] described the first case of chronic thyroiditis in a 41-year-old with benign cystic teratoma of the ovary. In their case, the patient had undergone a partial thyroidectomy for chronic thyroiditis. Hashimoto's disease was not specifically mentioned in the pathology report from the partial thyroidectomy. The patient was later found to have bilateral benign cystic ovarian teratomas. In the ovarian thyroid tissue, chronic thyroiditis was found consistent with Hashimoto's disease. Postoperative tests of thyroid antibody activity were negative.

In 1972, Watson[7] reported only one case of Hashimoto's disease of the thyroid component of a benign cystic ovarian teratoma after reviewing three hundred and fifteen cases of ovarian teratomas. In this cases, there was no prior thyroid surgery and the patient's thyroid exam was normal. Immunological investigations failed to demonstrate the presence of any thyroid-component antibodies one year after the operation.

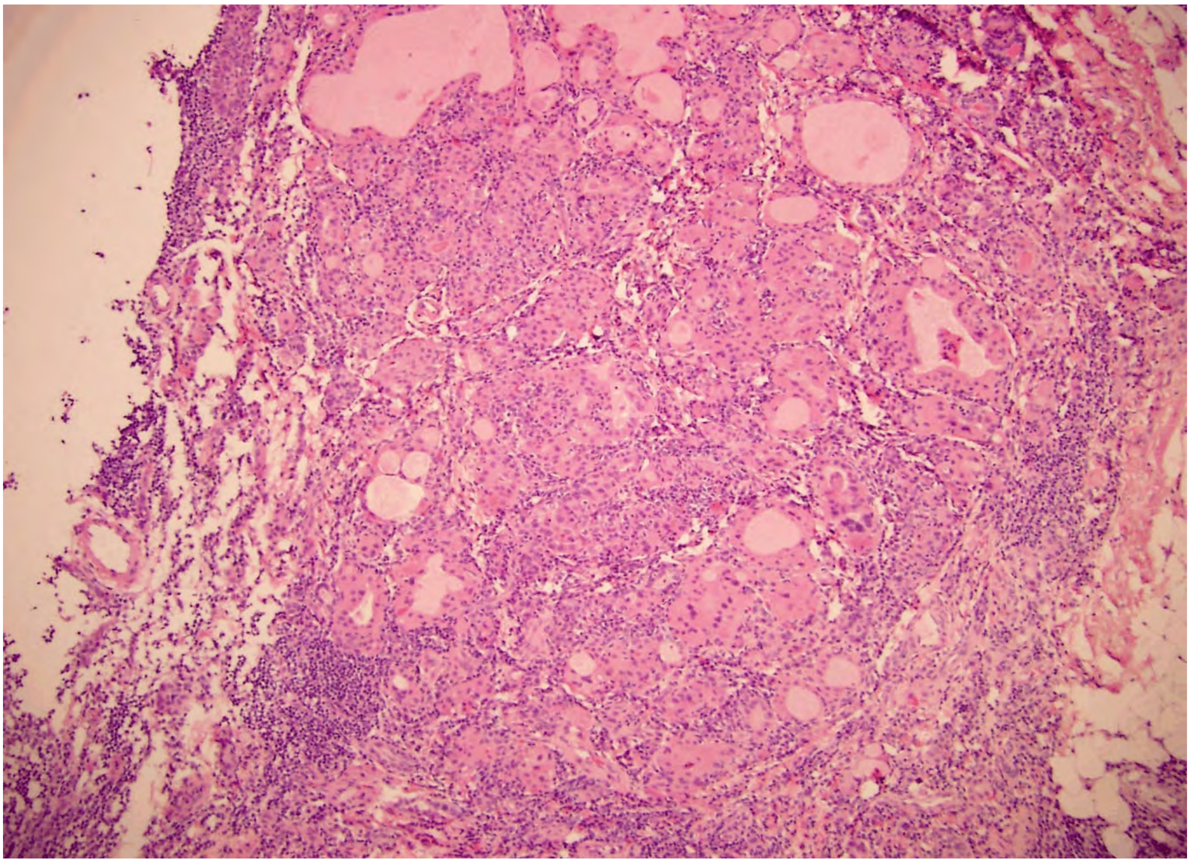

Figure 2. Photo labeled TTF1: Immunohistochemical stain for TTF-1 reveals positive nuclear staining, confirming thyroid origin.

In 1991, Farrell[8] reported a case of Hashimoto's disease in a benign cystic teratoma of an ovary in a 14-year-old with positive thyroid specific antibodies. In 1998, Fernando et al.[11] reported a case of histological autoimmune thyroiditis in struma ovarii, but Hürthle cells were not seen.

Carvalho in 2002[9] and Amareen in 2004[10] reported cases of Hashimoto's thyroiditis and frank hypothyroidism following the resection of struma ovarii tumors. We report the first case of Hashimoto's thyroiditis involving struma ovarii and a thyroid gland with Hürthle cells, positive antithyroid antibodies, but normal thyroid function.

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Thyroid Science 6(6)CR1-7, 2011

Hypothyroidism, Particularly Associated with Weight Loss: Evaluation and Treatment based on Symptoms and Thyroid Hormone Levels

(Full Text Free in pdf format)

Thomas Najarian, MD and Carol N. Rowsemitt, PhD, RN, FNP

Correspondence: Dr. Thomas Najarian, Incline Village, NV, tnajarianmd@hotmail.com
Correspondence: Dr. Carol Rowsemitt, San Luis Obispo, CA, rosey805@gmail.com

Abstract. Famine causes adaptive changes in thyroid function which helped individuals survive during times of low food availability. These changes in thyroid function and metabolism have become maladaptive as the induced hypothyroidism associated with intentional weight loss restricts the success of diet attempts and encourages weight regain. In our previous paper[1] we described the mechanisms and consequences behind maladaptive hypothyroidism associated with intentional weight loss. Here we give two specific patient examples of this syndrome and how the biochemical and clinical changes were managed for the clinical benefit of our patients. More broadly, we address the need to understand that there are limitations to our ability to detect every appropriate variable in any one patient, so that we do not overestimate the value of any particular lab reading in any one patient.

Keywords • Famine • Weight loss • Maladaptive hypothyroidism

Reference: 1. Rowsemitt, C.N. and Najarian, T.: TSH is Not the Answer: Rationale for a New Paradigm to Evaluate and Treat Hypothyroidism, Particularly Associated with Weight Loss. *Thyroid Science*, 6(6):H1-16, 2011.

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Thomas Najarian, MD and Carol N. Rowsemitt, PhD, RN, FNP

Correspondence: Dr. Thomas Najarian, Incline Village, NV, tnajarianmd@hotmail.com
Correspondence: Dr. Carol Rowsemitt, San Luis Obispo, CA, rosey805@gmail.com

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Abstract. Famine causes adaptive changes in thyroid function which helped individuals survive during times of low food availability. These changes in thyroid function and metabolism have become maladaptive as the induced hypothyroidism associated with intentional weight loss restricts the success of diet attempts and encourages weight regain. In our previous paper [1] we described the mechanisms and consequences behind maladaptive hypothyroidism associated with intentional weight loss. Here we give two specific patient examples of this syndrome and how the biochemical and clinical changes were managed for the clinical benefit of our patients. More broadly, we address the need to understand that there are limitations to our ability to detect every appropriate variable in any one patient, so that we do not overestimate the value of any particular lab reading in any one patient.

Keywords ● Famine ● Weight loss ● Maladaptive hypothyroidism

Introduction

As described in our previous paper, we find that assessment of patient symptoms, free thyroxine (FT_4), free 3,5,3'-triiodothyronine (FT_3), and 3,3',5'-triiodothyronine [reverse T_3 (rT_3)] is an effective approach to treating hypothyroidism, particularly that occurring during weight loss attempts. Our main rationale is that using thyroid stimulating hormone (TSH) as the primary determinant of thyroid function is misleading because the set point for circulating thyroid hormones is lowered in many patients in a hypocaloric state. A major consequence of weight loss is a change in thyroid function which is highly adaptive in a calorically restricted environment, but we consider to be maladaptive hypothyroidism in the context of our current environment of excess high fat, high calorie food, and little need to expend energy. These changes have been documented in other studies where thyroid function and basal metabolic rate have been measured in the presence of caloric restriction in humans and animals. See Rowsemitt and Najarian[1] for discussion and literature. A major concern of the authors is that a new era of medical treatment to control appetite and food cravings appears imminent, but that the accompanying weight loss-induced changes in thyroid function are not appreciated by most clinicians. We are not trying to raise a patient's metabolism above normal to generate weight loss; we are merely trying to return decreased metabolism to normal, thereby allowing a patient's weight loss behaviors to produce the desired effect. Not all weight loss patients suffer this decrease in metabolism. The clinician must evaluate symptoms and appropriate laboratory values to determine if treatment is needed.

Two other issues remain in addressing thyroid problems in the hypocaloric state: (1) Most recent studies discount the value of T_3 treatment.[2] We are taught that the prohormone T_4 is converted to adequate amounts of T_3, the active hormone, so that there is no need to administer T_3. T_3, which we believe is critical for treating our patients with maladaptive hypothyroidism, is not even available in pill form in the formulary of the United Kingdom Health Care System. Only T_4 is covered for treatment of hypothyroidism; T_3 is covered only as an injectable for myxedema coma, a severe form of hypothyroidism.[3] (2) We find that rT_3 has been discredited by most fellow clinicians. In this paper, we present our own clinical experience which demonstrates the importance of both T_3 and rT_3 for the evaluation and treatment of the hypothyroidism which occurs in many people during weight loss attempts.

In most studies of weight loss, whether with medications, bariatric surgery, or any other approach, a plateau in weight often occurs in the first six months of treatment, sometimes with weight regain even while on treatment.[4,5] Along with any weight loss approach, symptoms of low thyroid are common. For example, bariatric surgery guidelines from the Mayo Clinic provide a list of possible symptoms during the first three to six months: "body aches, feeling tired, as if you have the flu, feeling cold, dry skin, hair thinning and hair loss, mood changes."[6]

The authors have the clinical experience over the past eight years of treating over 15,000 obese patients with a healthy low carbohydrate, low fat diet, supplements to correct any nutritional deficits from the low calorie diet, a program of light exercise, and various medications for appetite control used both on and off label. The weight loss in our clinic has averaged about 19% at 2 years for those who stay on treatment that long. Other benefits that we have observed with this treatment are improved blood pressure using fewer antihypertensive medications; improved glycemia, again with fewer anti-diabetic medications; improved lipids; and improved quality of life.

We also have patients who have come to us seeking help who believe they have hypothyroidism due to their understanding of their classic symptoms which may include: fatigue, depression, feeling cold or having cold hands and feet, constipation, hair loss, dry skin, heavy menstrual periods, and insomnia. They may also have raised diastolic blood pressure, partly due to vasoconstriction. Vasoconstriction with resultant cold extremities is one way that humans and animals preserve body mass during times of inadequate caloric intake by reducing both heat loss and energy expenditure. Some of these patients have been trying to lose weight and do not desire a medical treatment, but believe that our approach to thyroid therapy will help them in their weight loss and maintenance attempts. These patients have struggled for years with signs and symptoms of hypothyroidism but have been repeatedly told by providers that their thyroid function is fine, based on TSH values. In these cases, providers have been bound by the conventional wisdom that TSH is the best tool to assess thyroid function. We feel this is extremely unfortunate because the providers are practicing in a manner they consider safe and appropriate while the patients feel insulted and stymied. Numerous patients have come to us with food diaries with the exact, measured amounts of what they have been eating for months, while getting some exercise. They report feeling demeaned by providers who clearly think they are keeping inaccurate food records. While this may be true in some cases,[7] many of our patients with a history of careful diary-keeping have found weight loss to be possible with our thyroid treatment.

We have seen these changes take place in thousands of weight loss patients. Many, but certainly not all patients, in our practice suffer from symptoms of maladaptive hypothyroidism. Initially, treatment with T_4 was tried, but failed to resolve the symptoms of hypothyroidism. Adding T_3 helped, but due to its expense, we replaced synthetic T_4 and T_3 with desiccated thyroid. Although many providers believe that the contents of desiccated thyroid are not well regulated, USP regulations are maintained with a ratio of T_4:T_3 of 4.22:1, such that 120 mg of desiccated thyroid contains 68.2 mcg T_4 and 17.8 mcg T_3.[8] Our procedure was to assess FT_4 and FT_3 levels several weeks into treatment. If a patient had low thyroid symptoms with low or borderline low hormone levels, we prescribed desiccated thyroid, with one-half dose for six days, then full dose. Dosage was dependent on age, symptoms, and hormone levels, but the usual full dose is 120 mg. Many patients do well on this treatment.

For many years we treated with desiccated thyroid with considerable success. However, for some patients, even treating to a borderline high level of FT_3 proved insufficient to eliminate hypothyroid symptoms including the weight plateau. Regardless of how hard they reported working out and limiting calories, the weight would not budge. While people attempting weight loss often eat more than they realize,[7] we do not believe this explained what was occurring with these patients. These were people with a history of success with us using medication to help with appetite and cravings, and who were known to have habits which tend to be more successful for weight loss and maintenance.[9]

When we became aware of the possible role of rT_3, we ran this assay on a patient with the problems described here and found her rT_3 to be 499 pg/mL (range: 90-350 pg/mL). Although rT_3 is commonly discounted as inactive, there is evidence for its binding to membrane receptors[10] and producing hypometabolic effects.[11] Given our increased understanding, we started to assess this parameter routinely. In some cases, lab results revealed a low FT_3 and an increased rT_3. For these patients, we correct the metabolic and thyroid functions using only T_3 in divided doses until the rT_3 is low normal. We then continue to use only T_3 if the patient is doing well clinically. (FT_3 will usually be in the normal range while FT_4 is low.) Alternatively, if the patient still has symptoms of low thyroid, even when FT_3 is normal or high normal and rT_3 and FT_4 are below normal, we add a low dose of T_4.

After treatment with T_3 or a combination of T_3 with T_4, and after the patient is clinically euthyroid with normal values of FT_3, FT_4 and rT_3, we often find that TSH is below normal. We believe that this is because the set point for feedback of thyroid hormones has been decreased. Thus, the body acts as though the thyroid gland is over-active during the weight loss state in order to lower metabolism and prevent weight loss during caloric restriction. When thyroid function is corrected with T_3, the already decreased TSH production is turned off, just as the TSH would be if one gave thyroid hormone to a euthyroid patient. (For further discussion, see Rowsemitt and Najarian.[1])

The following case reports from our practice should help to delineate this hypothesis in actual practice. For thyroid testing, all patients are instructed not to take their morning dose of thyroid medication until after a morning blood sample. Symptoms of high thyroid are explained to the patient; the patient is advised to call our practice immediately for medication adjustment should any of these symptoms arise. Patients are also advised that a sudden increase in food intake can cause their own thyroid glands to increase hormone production, causing hyperthyroid symptoms.

Case Reports

Patient Number 1. The first patient example is a 67-year-old female; height: 5’2”; weight: 268 lbs; body mass index (BMI): 49 (range: 19-24; overweight; 25-29; obesity: ≥ 30). Baseline blood pressure was 110/74, blood sugar (BS) was 153 mg/dL 10 days after her first visit. Her medical problems at baseline included obesity, type 2 diabetes mellitus (DM2), high blood pressure (HTN), fatigue, depression, and asthma. Her medications included glipizide 10 mg daily, amitriptyline 50 mg daily, metoprolol 50 mg daily, furosemide 40 mg daily, potassium chloride, lisinopril 10 mg daily, Advair Discus 500/50 twice daily (bid), and montelukast 10 mg daily.

She was started on our comprehensive program. Five months after starting her weight loss treatment, she developed symptoms of hypothyroidism with constipation and fatigue. She had lost 28 lbs by this time and was having difficulty losing more weight even though she was eating less than she was before her weight loss treatment began. At the start of treatment, her FT_4 was 0.9 ng/dL (range: 0.7-1.48). At the time of her low thyroid symptoms, her FT_3 was 2.9 pg/mL (range: 1.71-3.71) and her FT_4 was 0.91 ng/dL (range: 0.7-1.48). She was then treated with thyroid hormone (desiccated thyroid with a ratio of T_4:T_3 of about 4:1) at 60 mg daily for 6 days to acclimate, then increased to 120 mg daily. Since her low thyroid symptoms were only partially improved, her thyroid hormone dose was increased to 150 mg daily 5 months later, with resolution of the constipation and fatigue. After two years on her weight loss treatment, her weight was 231 lbs. Nearly 3 years after the start of her weight loss treatment, while on 150 mg of thyroid hormone, she felt cold and constipated, with another weight loss plateau. We had just started testing for rT_3 at this point. Her labs on the 150 mg dose of desiccated thyroid were: rT_3 394 pg/mL (range: 90-350), FT_3 3.94 pg/mL (range: 1.71-3.71), and FT_4 1.24 ng/dL (range: 0.7-1.48). The task of bringing down her rT_3 was then addressed. Over a period of a few months, her desiccated thyroid hormone was discontinued and instead the patient was given gradually increasing doses of T_3 only, starting at 20 mcg daily and gradually increasing the T_3 to 60 mcg bid. Five months after starting on T_3 with increasing doses, her weight had dropped to 209 lbs. Her BP was 118/66 mmHg with pulse of 74 on lisinopril 10 mg daily, metoprolol 50 mg bid, and furosemide 40 mg daily. Instead of glipizide, she was taking metformin 500 mg bid. She was clinically euthyroid on the T_3 only. Her most recent labs on 60 mcg bid of T_3 were FT_3 3.8 pg/mL (range: 1.71-3.71), FT_4 0.64 ng/dL (range: 0.7-1.48) and rT_3 137 pg/mL (range: 90-350). Four months prior to this visit her BS was 125 mg/dL.

Comments. This example makes the important point that three years into the program, with FT_3 above normal and FT_4 in the reference range, the patient had difficulty losing weight and had low thyroid symptoms. We believe that this was due to her elevated level of rT_3. The only way to lower rT_3 in this setting is to avoid giving any T_4 (since T_4 is the source of both T_3 and rT_3) and to replace T_4/T_3 with T_3 only. Over a period of a few months, both the rT_3 and T_4 will fall while the T_3 should remain in the normal range.

Another point is that there are wide reference ranges for thyroid tests. Some patients feel optimally well when their thyroid levels are on the high side and some when the thyroid levels are lower in the normal range. For example, a patient with a history of an anxiety disorder or sensitivity to stimulants such as caffeine may feel better when thyroid levels are on the low sides of their ranges. Some require treatment at the high end of normal to eliminate constipation, cold extremities, and/or other symptoms of low thyroid. We think that optimizing symptoms is a good guide along with complete thyroid testing including FT_4, FT_3, and rT_3, especially during caloric restriction. One can optimize symptoms of constipation or diarrhea, feeling too cold or hot, depression or anxiety, or feeling fatigue (which can result from high or low thyroid), etc., by appropriate dosing of T_3 with or without T_4.

Patient Number 2. The second patient example is a 46 year old female, 5’2”, weight 150 lbs, BMI 28 (range: 18.5-24.9; overweight 25-29.9; obesity ≥ 30), with HTN. Her blood pressure was slightly elevated at 148/85 (on lisinopril 5 mg daily). Her medical problems at baseline included history of Hashimoto’s thyroiditis, borderline high TSH, elevated lipids, and HTN. Her medications were lisinopril 5 mg daily, estradiol 2 mg daily, and rofecoxib 25 mg daily for osteoarthritis of her large joints. She was started on our comprehensive program. Thyroid treatment was started as well because of initial low thyroid symptoms of fatigue, constipation, and feeling cold along with a TSH of 3.41 uIU/mL (considered elevated by some, but not all groups who set limits for TSH). Desiccated thyroid was prescribed at 60 mg for six days to adjust to the medication, and then advanced to 120 mg daily. Over a period of several years thyroid hormone dose was reduced to 45 mg as dictated by clinical and lab results, and she was feeling relatively well. Her weight remained between 119 lbs and 130 lbs. Her blood pressure and pulse remained in the normal range (100/60-138/78, pulse 64-72) with no antihypertensive medications. Four years into her treatment, desiccated thyroid became unavailable so she was switched to levothyroxine at 75 mcg daily. Within a few weeks she began to feel tired, cold, and depressed and developed constipation and hair loss. Her FT_3 was 2.3 pg/mL (range: 2.2-4.0), FT_4 1.07 ng/dL (range: 0.93-1.70), and TSH was 0.91 uIU/mL. Her levothyroxine was increased to 100 mcg daily and T_3 was added at 5 mcg bid. Two months later, her first test of rT_3 was 379 pg/mL (range: 90-350), FT_4 1.12 ng/dL (range: 0.93-1.70), FT_3 2.4 pg/mL (range: 2.2-4.0). Over the next 4 months her levothyroxine dose was gradually reduced to zero, and she was placed on gradually increasing doses of T_3 only, ending on 25 mcg bid. Her weight was 125 lbs, BP 122/80 on no medications, and pulse was 72. She no longer suffered from hair loss; her bowels were normal, she felt well, and she stated that for the first time in her life she was not cold. Her lipids were also improved compared to baseline. On this regimen her rT_3 was 193 pg/mL (range: 90-350), FT_3 2.5 pg/mL (range: 2.2-4.0), and FT_4 0.67 ng/dL (range: 0.93-1.70).

Comments. This patient failed to achieve her optimum health until her rT_3 was mid-normal on T_3 replacement only. In addition, correcting peripheral vasoconstriction results in improved comfort, better sleep, and improved blood pressure, especially diastolic blood pressure. Patients with untreated hypothyroidism may have elevated blood pressure, especially diastolic hypertension, due to peripheral vasoconstriction. After the T_3 treatment to reduce rT_3 levels, a change from T_3 to desiccated thyroid or other ratio of T_4:T_3 dosing would be an option.

Discussion

By the early 1970’s, TSH became the gold standard for assessing thyroid function. Part of its prominence as a diagnostic tool appears to have arisen because TSH levels change logarithmically when the levels of circulating thyroid hormones are higher or lower than the set point. However, several issues of basic endocrinology allow one to realize that using TSH alone will have severe limitations. TSH levels will not necessarily distinguish secondary hypothyroidism (of pituitary cause) from normal. A PubMed search of (intracellular) thyroid receptor mutations produced 598 citations and a search for mutations of the proteins which transfer thyroid hormones across cell membranes produced 65 citations. Clearly, this area of research is deemed important and these are only two portions of the pathway involved in generating a metabolic change via thyroid hormones. So assuming normal pituitary function, TSH does not really provide us with information about the desired result: metabolism. It only provides us with the information that the thyroid hormones are circulating at a level within the limits set by higher brain levels. As pointed out by Dr. David Derry:

> If you remember it was a long time before the medical profession admitted that there were two new diseases to appear in the world that were not there before. Chronic fatigue and fibromyalgia were non-existent before 1980. This is seven years after the 1973 consensus meeting. So where did these two new diseases come from? The symptoms and signs of chronic fatigue and fibromyalgia were described in the literature in the 1930's as one way that low thyroid could be expressed. Treated early it was easily fixed with thyroid in adequate doses. But even then the clinicians had noticed that if a patient has low thyroid (chronic fatigue and fibromyalgia) for too long then it became more difficult to reverse all signs and symptoms regardless of what they were.[12]

Clinicians have relied strongly on TSH. Yet there has been an ongoing discussion of what range should be considered normal. Prior to the TSH assay and availability of commercial levothyroxine, patients were treated with desiccated thyroid with the dosage increasing until signs and symptoms were resolved. So two things had changed: (1) newer treatment trends involved using lower doses of pure T_4 and (2) the active hormone, T_3, was not given directly to patients. As has been known for years, T_3 is less available in the hypocaloric state.[1]

Numerous studies of weight loss treatments (whether from very low calorie diets, weight loss medications and diet, or bariatric surgery) often list as side effects the same spectrum of symptoms such as fatigue, depression, constipation, hair loss, feeling cold, and insomnia. We believe the insomnia may be related to the coldness of the body core and/or extremities. Many of these symptoms are likely due to the diet-induced hypothyroidism which is maladaptive in our current environment. Testing TSH, FT_4 or total T_4 will miss the diagnosis, since the changes in metabolism and thyroid function consist of only a slight lowering of TSH. Reported changes in total T_4 and FT_4 are inconsistent.[1] If the appropriate labs are run, an increase in rT_3 is found, accompanied by a decrease in FT_3. The syndrome of hypocaloric-induced hypothyroidism can be diagnosed only by evaluating changes in rT_3 and FT_3 as well as careful assessment of thyroid symptoms. Correction of diastolic hypertension, improvement of lipids and clinical symptoms, with return of rT_3 and FT_3 to normal after replacement of T_3 will confirm that the condition was present and treated appropriately. While many clinicians discount rT_3, our clinical results show its importance for patients whose systems use this pathway to decrease metabolism.

The assessment of thyroid status in clinical practice is generally based on a number which represents only one aspect of the system: a circulating hormone level. The clinician is not measuring the ability of that hormone to function by assessing metabolic rate or other signs and symptoms. A direct measure of metabolism would be a more meaningful approach. Since the symptoms are often vague, they may be dismissed by providers. In our litigious society, numbers give us comfortable boundaries with which to determine when to treat and when to tell a patient, "No, there's nothing wrong with your thyroid. If you are depressed, let's try an antidepressant. If you can't lose weight, try eating less and exercising more." We must also realize that there are false negatives and false positives for all tests, including lab tests. Thyroid function tests have a wide range of normal reference ranges. Reference ranges are determined by testing large numbers of "normal" patients and arbitrarily calling the highest 2.5% elevated and the lowest 2.5% as below normal.[13] Values outside these ranges often do not mean disease, and in fact may indicate improved health, such as an HDL level above normal. In certain mountainous areas in Europe with low iodine availability, cretins were born due to low thyroid hormones prenatally.[14] If such a population were used to determine the normal values of thyroid tests before the cause of cretinism was understood, the test population would have included the cretins. This would have produced reference lab ranges with lows for FT_4 and FT_3 that are considered markedly hypothyroid today.

When considering reference ranges for all of the thyroid labs, we find it particularly interesting that our patients with multiple low thyroid symptoms typically reach the low end of the ranges for FT_4 and FT_3; in some patients, these values go below the lower end of the range. To determine what values constitute the reference range, blood samples are obtained from clinically "normal" people. We have come to assume that many people included in the "normal" sampling are probably those in a hypocaloric state with some symptoms of low thyroid function. When you consider the percentage of people who are trying to lose weight at any point in time, this subset of the population must be skewing the reference range to include those who are actually mildly low thyroid by symptomatic criteria.

In addition to the information provided above, we have seen evidence of other adaptations to altered thyroid hormone levels. Many patients will do fine when maintained on their initial dose of desiccated thyroid. However for others, after several months of treatment, the patient reaches a plateau of weight with the return of low thyroid symptoms. When lab values are obtained, these patients usually have FT_3 and FT_4 which have returned to their previously low pre-thyroid-treatment levels. This demonstrates the body's ability to increase degradation rates of T_3 and T_4 which the body recognizes as being at hyperthyroid levels in the face of a hypocaloric diet. Also, in patients with high rT_3 who have been treated with T_3 only, we generally add some T_4 to the T_3 treatment after rT_3 has decreased to normal levels. Anecdotally, we have noticed that some of our patients with the most challenging weight struggles are those whose rT_3 levels rise dramatically as soon as any T_4 is added to their T_3 dose.

In the larger view, we must accept the fact that scientific knowledge evolves over time and both our understanding of what should be measured and the meaning of the resultant measurements can change. Consider cholesterol. Initially, we assessed total cholesterol with higher levels indicating increased cardiovascular risk. As time went on, we learned of HDL-cholesterol and LDL-cholesterol. Limits were set for each, with higher HDL being protective and lower LDL healthier. As the years have gone on, further refinement of the cholesterol parameters have been elucidated as has the importance of inflammatory markers.[15] These refinements are based on clinical outcomes. We should fully expect to see changes in both the parameters assessed and their acceptable values as our understanding increases.

But we will never argue for the dominance of a lab test when signs and symptoms are available. In considering thyroid lab values, we must also be cognizant of known biochemical variants such as receptor and transporter abnormalities which may cause a lab result to be at odds with the signs and symptoms.

It is possible that lifestyle changes in our society have affected thyroid function so that our normal values might be different when compared to people who lived thousands of years ago. Among the environmental changes that may lead to differences in thyroid levels are the amount of food eaten (increases in weight may raise thyroid levels and decreases in weight may lower thyroid levels)[1] and ambient temperature (warmer environments such as heated living and working spaces may lower thyroid levels). It is possible that our "normal" values, especially for those who are trying to lose weight, are in fact lower than what would have been determined from a population of normal people from thousands of years ago. Our "normal" ranges for thyroid tests might tend to be misleading in the same way that testing a population of "normal" people in areas of iodine deficiency hundreds of years ago would have been misleading in guiding people who needed to be treated to improve individual health. Normal values needed to be based on more than two standard deviations outside the range of "normal" people. We need to critically look at the health of those "normals" to see whether a different reference range would better serve the health of our patients. Certainly clinical health must be taken into account as has been done in our evolving understanding of cholesterol and inflammatory markers for cardiovascular disease risk.

While we have arrived at our current approach to thyroid treatment by years of working with patients to find the best approaches, we believe the research community should address these issues with our findings in mind. Controlled experiments studying thyroid treatment during weight loss should be performed monitoring rT_3 and treating with this paradigm (T_3 treatment) versus both untreated control and thyroxine groups.

While 10% weight loss is helpful at decreasing co-morbidities such as hypertension and type 2 DM, attaining normal weight seems out of reach of many obese people. This is partly due to the plateau created by maladaptive hypothyroidism. Ideally, we would like to be able to help many patients reach and maintain normal weight. Given our current environment with freedom from vicissitudes of food availability, this goal is harder than it would otherwise be. In our experience of having a combination of medications to suppress appetite and enhance satiety paired with the ability to fight this weight retaining thyroid response, we have been able to assist many people to reach and maintain normal weight. We submit these ideas hoping that others will join us in re-evaluating thyroid treatment when maladaptive hypothyroidism occurs during weight loss attempts. Clinicians must use clinical skills and patient-centered concerns in the optimum evaluation and treatment of their patients and not succumb to blindly following an arbitrary system of defined normal lab values in making therapeutic decisions that greatly affect the well-being of their patients.

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Thyrotoxicosis in Pregnancy Complicated by Propylthiouracil-induced Hepatitis

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Lajya Devi, MD,[1A] Rimpy Tandon, MD,[2A]
Ibha Kumari, MD,[2B] Anju Huria, MD,[2C] Poonam Goel, MD[2D]

[1]Department of Obstetrics & Gynecology,
Guru Gobind Singh Medical College, Faridkot, Punjab
[1A]Associate professor, lajja.goyal@rediffmail.com.

[2]Department of Obstetrics & Gynecology,
Government Medical College & Hospital, Sector–32, Chandigarh
[2A]Assistant Professor, drrimpy@yahoo.com;
[2B]Ex-Senior Lecturer, kumari.ibha@yahoo.com;
[2C]Professor & Head, anjuhuria@yahoo.com;
[2D]Professor, poonam1302@yahoo.com

*Corresponding Author: Dr. Rimpy Tandon,
Assistant Professor, Department of Obstetrics & Gynecology,
Government Medical College & Hospital, Sector-32,
Chandigarh, drrimpy@yahoo.com

Abstract. Graves' disease is the most common cause of hyperthyroidism during pregnancy. Propylthiouracil (PTU) is the treatment of choice due to its relative safety during pregnancy compared to methimazole. However, rarely, PTU causes serious complications like hepatitis. We report a case of hepatitis possibly related to PTU during pregnancy complicated by thyrotoxicosis.

Keywords • Graves' disease • Hepatitis • Methimazole • Pregnancy • Propylthiouracil • Thyrotoxicosis

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Case Report

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Lajya Devi, MD,[1A] Rimpy Tandon, MD,[2A]
Ibha Kumari, MD,[2B] Anju Huria, MD,[2C] Poonam Goel, MD[2D]

[1]Department of Obstetrics & Gynecology, Guru Gobind Singh Medical College, Faridkot, Punjab
[1A]Associate professor, lajja.goyal@rediffmail.com.

[2]Department of Obstetrics & Gynecology, Government Medical College & Hospital, Sector–32, Chandigarh
[2A]Assistant Professor, drrimpy@yahoo.com; [2B]Ex-Senior Lecturer, kumari.ibha@yahoo.com;
[2C]Professor & Head, anjuhuria@yahoo.com; [2D]Professor, poonam1302@yahoo.com.

**Corresponding Author:* Dr. Rimpy Tandon,
Assistant Professor, Department of Obstetrics & Gynecology,
Government Medical College & Hospital, Sector-32, Chandigarh, drrimpy@yahoo.com

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Introduction

Hyperthyroidism complicates up to 0.2% of pregnancies, and Graves' disease accounts for 90%-to-95% of these cases.[1] Medical treatment with antithyroid drugs is the preferred mode of therapy in such situations, as radioactive iodine is contraindicated during pregnancy.[2]

Propylthiouracil (PTU) is the antithyroid drug often prescribed during pregnancy due to its relative safety compared to methimazole.[3] However, rarely, PTU causes serious complications. One complication is hepatitis that leads to a management dilemma. Withdrawing the drug results in a recurrence of thyrotoxicosis that may adversely affect the pregnancy.

Case Report

A 22-year-primigravida was seen at 5 weeks of gestation with complaints of palpitation, tremors, and excessive sweating. Examination revealed diffuse thyroid enlargement and ophthalmopathy. Her pulse was 110 beats per minute and her blood pressure was 150/90 mm of Hg. Her hemoglobin was 12 gm/dL (10.5-to-14 gm/dL) and other cell lines were also within their reference ranges. Baseline liver and renal function tests were within their reference ranges. Her TSH level was 0.2 U/mL (0.6-to-4.5 U/mL), her free T_3 was 6.3 pg/mL (1.2–to-4.1pg/mL), and her free T_4 was 2.96 ng/dL (0.7-to-1.72ng/dL). Thyroid ultrasonography showed that the gland was diffusely enlarged.

She was started on 50 mg of PTU and 20 mg of propranolol twice each day. Follow-up after 6 weeks revealed persistent symptoms; hence, her daily dose of PTU was increased to 300 mg. The patient finally achieved a euthyroid state with a PTU dose of 600 mg per day. Subsequent follow-ups of the patient till 32 weeks of gestation were uneventful.

At 33-weeks of gestation, jaundice was detected. Laboratory testing showed the following: a total serum bilirubin of 9.4 mg/dL (0.5-to-1.2 mg/dL), conjugated bilirubin of 7.8 mg/dL, serum aspartate aminotransferase of 302 IU/L (5-to- 40 IU/L), alanine aminotransferase of 325 IU/L (5-to-35 IU/L), alkaline phosphatase 344 IU/L (108-to-306 IU/L), and a prothrombin time index of 71% (75%-to-100%). There was no history of any preceding fever.

Viral markers for hepatitis A, B, C and E were negative and HIV serology was non-reactive. Ultrasonography of the patient's liver and gall bladder was unremarkable.

A diagnosis of PTU-induced hepatitis was made and PTU was withdrawn. The dose of propranolol was increased to 60 mg daily in three divided doses. Fetal well-being was monitored with daily non-stress testing and on alternate days a biophysical profile. Liver function tests showed improvement one week after the patient stopped the use of PTU. However, thyroid function test results showed a reversal of the hyperthyroid state: her free T_4 level was 3.5 ng/dL (0.7-to-1.72 ng/dL).

At 35-weeks of gestation, the patient complained of loss of fetal movement and features that revealed abruption. Intrauterine fetal death was confirmed with ultrasonography. Labour was induced and the patient delivered a dead fetus weighing 2.4 kg.

Two weeks after delivery, the patient developed palpitations and sweating. Her TSH was abnormally low. She was then treated with radioablation (5 mCi).

Six months after radioablative therapy, she conceived again in a euthyroid state. In the second month of pregnancy, she again developed features of Graves' disease. This time, her hyperthyroidism was controlled with 20 mg of NeoMercazole® twice daily. (NeoMercazole® is carbimazole, which is completely metabolised to methimazole, the metabolite that is responsible for the drug's clinical effects.) She tolerated the dose well and achieved euthyroid status quickly within 4 weeks. She was closely supervised till term and delivered a live and healthy baby weighing 2.6 kg at 37-weeks of gestation.

Discussion

The management of thyrotoxicosis in our patient raises important and pertinent issues. Uncontrolled thyrotoxicosis in pregnancy is associated with maternal and fetal complications. These include pre-eclampsia, thyroid crisis, preterm labour, abruptio placentae, and fetal death.[2]

Our patient's first pregnancy was complicated with abruptio placentae and still birth. These complications were possibly related to uncontrolled thyrotoxicosis after the patient stopped the use of PTU.

The second issue of importance is whether to use PTU or methimazole to control thyrotoxicosis during preganancy.[4] Both drugs have been used for this purpose. PTU is preferably used in many countries where methimazole is considered to be more often associated with fetal abnormalities like aplasia cutis, oesophageal atresia, choanal atresia, facial abnormalities, and mental retardation.[5] However, there is now a consensus that the overall risk of congenital abnormalities from methimazole is no higher than that reported from the use of nonteratogenic drugs.[5]

In our patient's first pregnancy, PTU was associated with hepatitis. However, methimazole produced no adverse reactions in the mother or the fetus.

The incidence of PTU-induced hepatitis ranges from 0.1%-to-0.2%.[6] It takes the form of allergic hepatitis accompanied by laboratory evidence of hepatocellular damage.[6] The occurrence of PTU-induced hepatitis in the third trimester of pregnancy leads to a treatment dilemma. Switching to other thionamides has been tried,[7] but this risks potential cross-reaction and hence should be avoided.[8]

Higher doses of PTU are associated with more adverse effects. Most often, hyperthyroidism during pregnancy is controlled with 100-to-450 mg of PTU. Occasionally, however, doses in the range of 600-to-800 mg/day are required. This is possibly related to poor compliance or altered PTU pharmacodynamics in pregnancy.

Surgery is the treatment option when persistently high doses of PTU are required or thyrotoxicosis remains uncontrolled. Surgery should preferably be performed in the second trimester.

Our case illustrates the fact that rare side effects of drugs used to control a medical condition in pregnancy may occur at any time. Hence, these patients' clinical condition should be closely monitored with liver function tests.

Our patient was interesting in one more aspect. She developed a hyperthyroid state soon after stopping PTU. Though after the delivery of the dead fetus in her first pregnancy, her hyperthyroid state was controlled with radioactive iodine. She then again developed thyrotoxicosis during her second pregnancy. This time, however, her hyperthyroidism was well controlled with methimazole and she delivered a healthy baby.

Conclusion

Hepatitis is a rare side effect of PTU, and its occurrence during pregnancy leads to a management dilemma. However, if hepatitis occurs in the second trimester, the option of surgery can be carried out. The available literature indicates that the patient can also safely use methimazole as was seen in our patient during her second pregnancy.

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Thyroid Science 6(1):1-3, 2011

Grave's Ophthalmopathy in the Absence of Abnormal Thyroid Hormone and Thyrotropin Levels and Thyrotropin Receptor Antibody

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Hidekatsu Yanai[1] and Hiroko Yamazaki[2]

[1]Department of Internal Medicine,
National Center for Global Health and Medicine,
Kohnodai Hospital, Ichikawa, Chiba 272-8516, Japan.

[2]Department of Ophthalmology,
National Center for Global Health and Medicine,
Kohnodai Hospital, Ichikawa, Chiba 272-8516, Japan.

Corresponding author: Hidekatsu Yanai, M.D., Ph.D., F.A.C.P.,
The Head, Department of Internal Medicine, National Center for Global Health and Medicine,
Kohnodai Hospital, Ichikawa, Chiba 272-8516, Japan, dyanai@hospk.ncgm.go.jp

Abstract. The onset of Grave's ophthalmopathy is in most cases concomitant with the onset of hyperthyroidism. Grave's ophthalmopathy and Graves' hyperthyroidism are closely associated and thought to be caused by thyrotropin receptor antibodies. Here we will show a patient with Grave's ophthalmopathy demonstrated by magnetic resonance imaging, but who showed normal thyroid hormone and thyrotoropin levels and the absence of thyrotropin receptor antibodies. Interestingly, the patient was seen on two occasions 10 years apart with a similar clinical presentation. During the patient's second evaluation, she was found to be positive for thyroid stimulating antibodies; this was the only indication for diagnosing the patient as having Graves' disease.

Keywords • Grave's ophthalmopathy • Hyperthyroidism • Thyrotropin receptor antibody • Thyroid stimulating antibody

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Case Reports

Grave's Ophthalmopathy in the Absence of Abnormal Thyroid Hormone and Thyrotropin Levels and Thyrotropin Receptor Antibody

Hidekatsu Yanai[1] and Hiroko Yamazaki[2]

[1]Department of Internal Medicine,
National Center for Global Health and Medicine,
Kohnodai Hospital, Ichikawa, Chiba 272-8516, Japan.
[2]Department of Ophthalmology,
National Center for Global Health and Medicine,
Kohnodai Hospital, Ichikawa, Chiba 272-8516, Japan.

Corresponding author: Hidekatsu Yanai, M.D., Ph.D., F.A.C.P.,
The Head, Department of Internal Medicine, National Center for Global Health and Medicine,
Kohnodai Hospital, Ichikawa, Chiba 272-8516, Japan, dyanai@hospk.ncgm.go.jp

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Abstract. The onset of Grave's ophthalmopathy is in most cases concomitant with the onset of hyperthyroidism. Grave's ophthalmopathy and Graves' hyperthyroidism are closely associated and thought to be caused by thyrotropin receptor antibodies. Here we will show a patient with Grave's ophthalmopathy demonstrated by magnetic resonance imaging, but who showed normal thyroid hormone and thyrotoropin levels and the absence of thyrotropin receptor antibodies. Interestingly, the patient was seen on two occasions 10 years apart with a similar clinical presentation. During the patient's second evaluation, she was found to be positive for thyroid stimulating antibodies; this was the only indication for diagnosing the patient as having Graves' disease.

Keywords Grave's ophthalmopathy • Hyperthyroidism • Thyrotropin receptor antibody • Thyroid stimulating antibody

Introduction

Grave's ophthalmopathy (GO) is one of complications of Graves' disease, which reduces the quality of life of patients with Graves' disease. The onset of GO in most cases concomitant with the onset of hyperthyroidism.

GO has been found to be closely associated with Graves' hyperthyroidism by the same autoimmune process. Thyrotropin receptor antibody (TRAb) is the likely candidate. This is likely because TRAb causes Graves' hyperthyroidism. Also, TRAb appears to be present in the orbital tissues, and the expression of TRAb is augmented in orbital tissues from patients with GO.[1] Here we report a patient with GO, who had reference range thyroid hormone and thyrotropin (TSH) levels and was negative for TRAb. Furthermore, the patient was seen on two occasions 10 years apart with a similar clinical presentation.

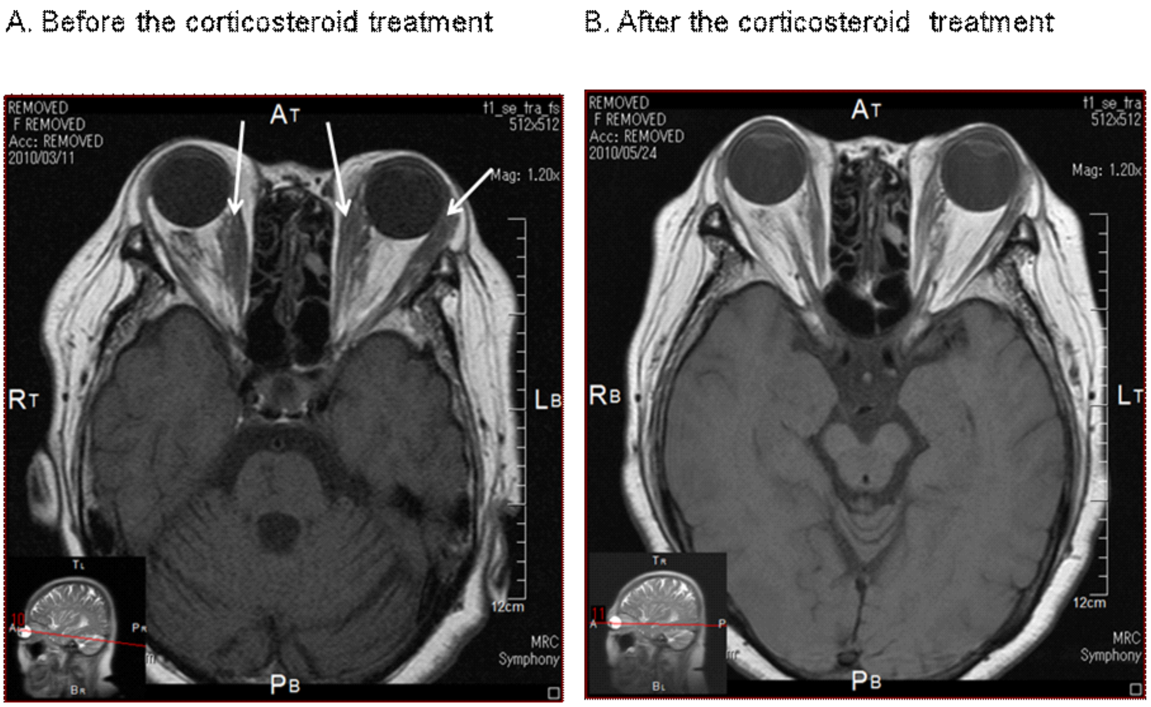
Case Report

A 65-year-old woman visited our hospital because of worsening of bilateral eye proptosis and corneal abrasion. At 56 years of age, she also visited our hospital because of proptosis, and her thyroid function was examined. Serum levels of free triiodothyronine and free thyroxine were 3.3 pg/mL (2.47-to-4.34 pg/mL) and 1.33 ng/dL (0.97-to-1.79 ng/dL), respectively, and her TRAb level was 0% (< 15%). She had not received treatment for Grave's disease and GO.

In March 2010, the patient revisited our hospital because of the progression of bilateral proptosis. T1-weighted magnetic resonance imaging (MRI) revealed enlarged eye muscles (Figure 1A), suggesting the existence of GO. She was diagnosed as having GO by an ophthalmologist and referred to our department.

Again, her thyroid function tests results were within their reference ranges: free triiodothyronine (2.96 pg/mL; reference range, 2.39-to-4.06 pg/mL), free thyroxine (1.13 ng/dL; reference range, 0.71-to-1.52 ng/dL), and TSH level (1.35 μIU/mL; reference range, 0.54-to-4.26 μIU/mL). Her TRAb level was also within its reference range (0%; reference range < 10%). Anti-thyroglobulin antibody and anti-microsomal antibodies were also negative.

During this second patient visit, we measured her thyroid stimulating antibody (TSAb) and found that it was positive (221%; reference range < 180 %). With this test results, she was finally diagnosed as having GO ten years after the onset of her GO. She


A. Before the corticosteroid treatment

B. After the corticosteroid treatment

FIGURE 1. Magnetic resonance imaging of Graves' ophthalmopathy before (A) and after (B) corticosteroid treatment. Arrows indicate enlarged eye muscles.

was treated with 30 mg of prednisolone orally each day. This corticosteroid treatment ameliorated her GO in 10 weeks (Figure 1B).

Discussion

The onset of GO in most cases is concomitant with the onset of hyperthyroidism. GO may present before the development of thyrotoxicosis, concomitant with thyrotoxicosis, or after the treatment of thyrotoxicosis. However, our patient had not shown the development of thyrotoxicosis, and also had not yet received treatment for Grave's disease for ten years after the development of GO.

Previously, the prevalence of patients without elevated free thyroxine and free triiodothyronine levels was been determined in 1,020 patients with GO.[2] The incidence was very rare (19 cases, 1.9%) among patients with GO.[2] Among 19 GO patients who did not show elevated serum free thyroxine and free triiodothyronine levels, only 7 patients (0.7%) her reference range TSH levels, and TRAb was detected in all patients.[2] However, in addition to having reference range serum free thyroxine, free triiodothyronine, and TSH levels, our patient was absent of TRAb. Tobacco smoking, radioactive iodine treatment, hyper- and/or hypothyroidism, elevated TRAb level, which were considered as risk factors for the development of GO,[3,4] were not observed in our patient.

The only abnormal laboratory finding in our patient was elevated TSAb. Nishikawa M, et al. evaluated the association between eye changes and thyroid-associated autoantibodies. They found that TSAb in Graves' patients with GO was significantly higher than that in patients without GO. They also found that the level of stimulating activity in Graves' patients with GO was significantly positively correlated with the sum of the swelling ratios of the individual eight eye muscles measured using MRI.[5] This result is evidence of a significance of TSAb in the development of GO.

Conclusion

We evaluated a GO patient with normal thyroid hormone and TSH levels and an absence of TRAb. To our knowledge, our observation is the first report to show that untreated GO for ten years was subsequently ameliorated by corticosteroid treatment. The only laboratory basis for diagnosing this patient as having Graves' disease was her positivity for TSAb. Her case warrants the study TSAb levels in other euthyoid, TRAb-negative GO patients.

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—Dr. John C. Lowe, LLC, Editor-in-Chief

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The Role of iodine in the Thyroid Status of Mothers and Their Neonates

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Rabindra Nath Das

Department of Statistics, The University of Burdwan, Burdwan, West Bengal, India

Correspondence: Dr. R.N. Das, Associate Professor, Department of Statistics,
The University of Burdwan, Burdwan, W.B., India; E-mail: rabindasbwn@yahoo.co.in

Dr. John C. Lowe's Editorial Introduction to Prof. Das' Paper

Abstract. It is well known that iodine is an indispensable component of thyroid hormones. The discovery of iodine deficiency and its adverse effects upon human beings is an instructive example of the transfer of scientific and medical knowledge to the benefit of the public health. Physicians have known for more than a century that deficient iodine intake is associated with endemic goiter, cretinism, and that it increases neonatal mortality. In this paper, statistical analysis is used to objectively verify the mathematical relationships of deficient maternal urinary iodine to the results of thyroid function tests (T3, T4, and TSH) of both low-iodine mothers and their neonates. In general, complex functional systems, such as human physiological mechanisms, are more easily interpreted based on true mathematical models. The mathematical relationships of the multiple variables analyzed in this paper are established by the statistical method of joint generalized linear modeling. The results of the statistical analysis are highly relevant to the diagnostic and therapeutic practices of clinicians who attend to pregnant women, their in utero embryos and fetuses, the women’s neonates after delivery, and by extension, the developmental (especially neurological) well-being of the offsprings as they mature. The analysis establishes relationships important to the health and well-being of both mothers and their neonates; simultaneously, it shows the exceptional utility of the statistical method of joint generalized linear modeling.

Keywords Hyperthyroidism • Hypothyroidism • Iodine • Joint generalized linear model • Structured dispersion • Thyroid functions • Urinary iodine excretion

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The Role of iodine in the Thyroid Status of Mothers and Their Neonates

Rabindra Nath Das

Department of Statistics, The University of Burdwan, Burdwan, West Bengal, India

Correspondence: Dr. R.N. Das, Associate Professor, Department of Statistics,
The University of Burdwan, Burdwan, W.B., India; E-mail: rabindasbwn@yahoo.co.in

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Introduction

Iodine is an essential component of thyroid hormones, and its importance stems mainly from that role. The most obvious consequence of iodine deficiency is goiter. This adaptive response is mediated principally by serum thyroid stimulating hormone (TSH). As the quantity of thyroid hormone reaching the pituitary thyrotrophic cells decreases, the cells are disinhibited and increase their synthesis and secretion of thyroid hormone. The increased TSH stimulates most functions of the thyroid gland. With too little iodine to synthesize enough thyroid hormone to suppress TSH secretion, the TSH remains high and stimulates hypertrophy of the thyroid gland. If the iodine deficiency is mild and the thyroid gland increases thyroid hormone production, the affected individual has no apparent consequence other than an enlarged thyroid.

In the past, when this disease entity was widespread among a particular population, it was labeled "endemic goiter." The disease was recognized as a significant public health issue. It received much less attention, however, than other pressing health problems such as infectious diseases. Cretinism is known to be associated with endemic goiter, but the existence of a continuum from mild mental retardation to gross neurological impairment has only been widely appreciated in the last several decades (see reviews by Delange et al.[1,2]).

The World Health Organization (WHO) recently increased its recommended iodine intake during pregnancy from 200-to-250 μg/L. WHO also suggested that a median urinary iodine concentration of 150-to-249 μg/L indicates adequate iodine intake in pregnant women. The TSH concentrations in blood collected from newborns 3-to-4 days after birth may be a sensitive indicator of even mild iodine deficiency during late pregnancy.[3,4]

The term "iodine deficiency disorders" serves to emphasize the many other consequences of iodine deficiency.[5] Of these disorders, disruption of reproductive function and damage to the developing fetus and infant are the most severe. Aspects of this topic have been reviewed in detail elsewhere.[6,7,8,9]

The International Council for Control of Iodine Deficiency Disorders (ICCIDD) recommends a daily intake of 100 μg iodine for nonpregnant adults[10,11,35,36] This number is based on studies of iodine accumulation and turnover, the T_4 dose required to maintain euthyroidism in athyreotics, T_4 disposal rates, and the amounts of iodine necessary to prevent goiter in populations.[11,12] Pregnant women need more than this baseline requirement to cover the iodine needs of the developing fetus and to compensate for increased renal iodine losses. In 2010, the ICCIDD recommended an intake of 200 μg for pregnant and lactating women.[11] Renal clearance of iodine increases during pregnancy;[13] in one study, for example, the concentration of iodine in the urine of women from a mildly iodine-deficient geographic area was 60% higher during pregnancy.[14]

Hypothyroxinemia, elevated serum TSH, enlargement of the thyroid gland (by 10% to 50%), and goiter are the most common measured consequences for the pregnant woman. However, these effects can be prevented by adequate iodine supplementation[12]

Iodine deficiency increases neonatal mortality. *We emphasize this statement so that iodine deficiency can take its proper place among the disorders that kill children*. "Child survival" is something of a buzzword in international aid circles, and showing its relation to iodine deficiency helps direct resources toward its correction.[15]

So far, many authors have conducted clinical and physiological studies of the effects of iodine on pregnant women and their neonates. But it is difficult to understand the functional relationships of iodine to mothers and their neonates based solely on clinical and physiological studies. In general, complex functional systems such as human physiological mechanisms are more easily interpreted based on true mathematical models.

Our literature search shows that a paucity of reports on the effects of iodine on mothers and their neonates are based on mathematical models. Recently, Das and Mukhopadhyay[16] reported using a mathematical model to study the effects of thyroid function, maternal urinary iodine, and neonatal weights.[16] However, we are aware of no studies based on mathematical models of the effects of iodine on the thyroid function of mothers and their neonates.

To fill this gap in the thyroidological research literature, this study derives the relationship between maternal urinary iodine excretion and the thyroid status of the mothers and their neonates. It also derives the relationship between the customary measures of the thyroid status of mothers and that of their neonates. This derivation allows the formulation of models that focus on the functional relationships between the maternal urinary iodine and the thyroid status of both mothers and their newborns.

The following sections of this paper cover log-normal and gamma joint generalized linear models, descriptions of the data, covariates, and response. Sections also display analyses and results, interpretation and discussion of the findings, and concluding remarks.

2. JOINT GENERALIZED LINEAR MODELS

Recently, log-normal and gamma models have become of interest in fitting data that arise from physiological studies.[16,17] It is well known that the gamma model with the constant coefficient of variation, and the log-normal model with constant variance, often give similar results.[23] However, in the analysis of physiological data, neither the coefficient of variation nor the variance needs to be constant, so that the two models do not necessarily give similar results.[17]

Das and Lee[18] have shown that for the analysis of data from quality-improvement experiments, the simple log-transformation may not be sufficient for stabilizing the variance. As a result, a further structured dispersion model is required. This, however, results in different optimal settings. Furthermore, with structured dispersion, there is no reason that the two models will give parameterizations with a common interpretation.[18] In general, continuous positive measurements belong to exponential and gamma distributions; they may have variance-to-mean relationship, and the variance of the response is non-constant. For heteroscedastic data, the log-transformation is often recommended for stabilizing the variance,[24] but in practice the variance may not always be stabilized (Myers et al.: Table 2.7).[21,p.36] For example, when

$$E\left(Y_i\right)=\mu_i \text{ and } Var\left(Y_i\right)=\sigma_i^2\mu_i^2,$$

the transformation $Z_i = \log(Y_i)$ gives stabilization of variance $Var\ (Z_i) \approx \sigma_i^2$.

However, if we want a parsimonious model, we may need a different transformation. Thus, a single data transformation may fail to meet various model assumptions. Nelder and Lee[22] proposed to use joint generalized linear models (JGLMs) for the mean and dispersion.

When the response Y_i is constrained to be positive, we often use a log transformation $Z_i = \log Y_i$. Under the log-normal distribution, we have a joint modeling of the mean and dispersion such that

$$E\ (Z_i) = \mu_i,\ Var\ (Z_i) = \sigma_i^2,$$

and

$$\mu_i = \mathbf{x}_i^t\beta,\ \log\ (\sigma_i^2) = \mathbf{g}_i^t\gamma, \qquad (2.1)$$

where x_i^t is the row vector for the regression coefficient β in the mean model, and g_i^t is the row vector for the regression coeffcient γ in the dispersion model.

Lee and Nelder[19] studied the estimation of joint modeling of the mean and dispersion. They proposed to use the maximum likelihood (ML) estimator for the mean parameters β and the restricted maximum likelihood for the dispersion parameters γ. The restricted likelihood estimators have proper adjustment of the degrees of freedom by estimating the mean parameters, which is important in the analysis of data from quality-improvement experiments because the number of parameters of β is often relatively large compared with the total sample size.

Nelder and Lee[22] propose a gamma modelling approach using whole data y_i. They advocate the use of joint generalized linear models:

$$E(y_i) = \mu_i \text{ and } Var(y_i) = \sigma_i^2 V(\mu_i),$$

where $V(\cdot)$ is the variance function and σ_i^2's are the dispersion parameters. In generalized linear models, the variance consists of two components, $V(\mu_i)$ is the one depending upon the changes of the mean and σ_i^2 is the one independent of mean adjustment. Instead of defining the two summarizing statistics as responses, they advocate modeling the mean and dispersion parameters jointly as follows:

$$\eta_i = g(\mu_i) = \mathbf{x}_i^t \beta \quad \text{and} \quad \xi_i = h(\sigma_i^2) = \mathbf{w}_i^t \gamma, \tag{2.2}$$

where $g(\cdot)$ and $h(\cdot)$ are generalized linear model link functions for the mean and dispersion, respectively and x_i^t and w_i^t are the row vectors for regression models based on the levels of control variables. For the estimation they propose to use the maximum likelihood (ML) estimators for the mean model and restricted ML (REML) estimators for the dispersion model.

In generalized linear models, the variance function characterizes the distribution of the generalized linear model family. For example, the distribution is normal if $V(\mu) = 1$; Poisson if $V(\mu) = \mu$; gamma if $V(\mu) = \mu^2$; etc. A more extensive discussion of generalized linear model approaches are given in Das and Lee,[18] Lee and Nelder,[19,20] Lee et al.[31] Lesperance and Park,[34] Qua et al.[33]

3. Data, Covariates, and Responses

Recently, Das and Mukhopadhyay[16] studied the effects of maternal urinary iodine, the mothers' and their neonates' thyroid hormone status, and the neonates' birth weights. The analyses were based on data collected by Chakraborty et al.,[25] as are the analyses in this paper. The description of the data set is given in Chakraborty et al.[25] and Das and Mukhopadhyay.[16] For ready reference, the study subject data set is as follows:

The data of Chakraborty et al.[25] is hospital-based, non-interventional, and cross-sectional. The 300 observed pregnant women who were in > 36 weeks of gestation; they were within the reproductive age group of 15-to-45 years. The women were admitted to the Gynaecology and Obstetrics Department of Burdwan Medical College and Hospital, Burdwan, West Bengal, India. Also studied were the respective neonates born to them during one calendar year (from May 2003 to May 2004). This study considered only pregnant women who suffered from iodine deficiency.

Data were collected on 8 variables. These included maternal urinary iodine excretion, T_3 (MT_3 say) T_4 (MT_4 say), and TSH (*MTSH* say). Neonate birth weights (y) and their T_3 (CT_3 say), T_4 (CT_4 say), (*CTSH* say) levels were also measured.

Maternal blood was collected from the cubital vein of the forearm for serum TSH assay. The neonatal blood was collected from the umbilical cord for neonatal serum TSH assay. Urinary iodine was assayed in the samples by the wet digestion method based on the 1937 principle of the Sandell and Koltho® reaction[29] and the method suggested by Dunn et al.[30]

We do not present the data set here, as it would substantially increase the length of the paper. However, we will submit our data set on request for verification of our analysis.

4. Analysis and Results

The aim of this study is the analysis of the relation of material urinary iodine to thyroid function test results of both mothers and their neonates. Log-normal and gamma models[21] are highly relevant to fitting positive data that arises from quality-improvement experiments. Das and Lee[18] have studied positive data for quality-improvement experiments. In doing so, they used log-normal and gamma models with joint generalized linear models. In addition, Das and Mukhopadhyay[16] modeled neonatal weights based on log-normal and gamma models. And recently, Das[17] studied human biochemical parameters based on log-normal and gamma models.

To understand the relationship of maternal iodine to the mothers' and their neonates' thyroid status, we had to derive the following models:

(i) Model of maternal urinary iodine excretion (response) on the mothers' thyroid hormone and their TSH levels (covariates).

(ii) Model of maternal urinary iodine excretion (response) on neonates' thyroid hormone and TSH levels (covariates).

(iii) Model of mothers' thyroid hormone levels.

(iv) Model of neonates' thyroid hormone levels.

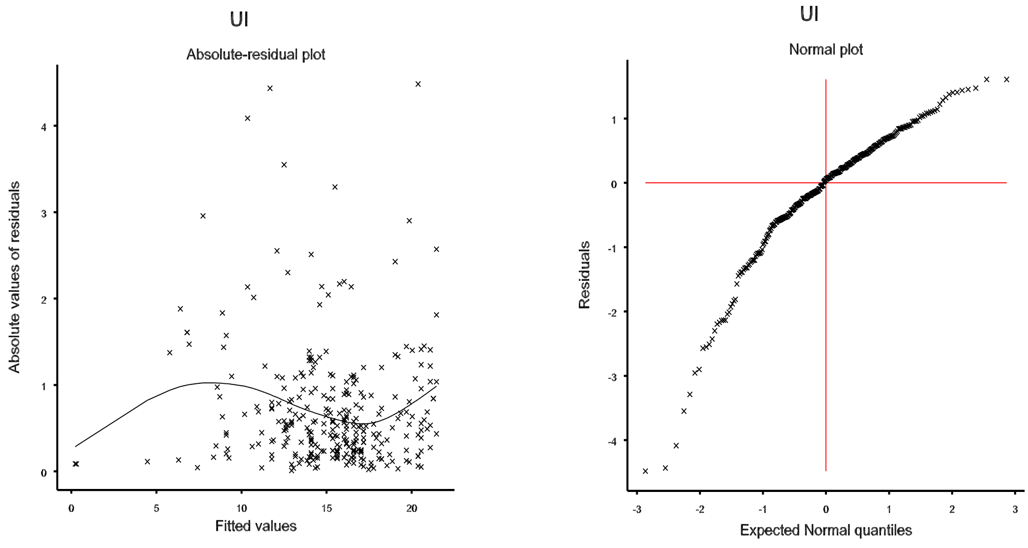
(v) Model of neonatal weights (response) on maternal urinary iodine excretion and mothers' and her neonates' thyroid hormone and TSH levels (covariates).[16]

We derived first four models above, and the fifth model was derived by Das and Mukhopadhyay.[16] These models were derived based on comparisons of log-normal and gamma model. We have selected the best one by comparison of both the models. Log-normal and gamma models are derived based on formulae (2.1) and (2.2), respectively. Final models are displayed, and the comparisons are as in Das and Mukhopadhyay.[16]

As noted above, data were collected on 8 variables. These included maternal urinary iodine excretion, MT_3, MT_4, and *MTSH*, and neonate birth weights (y) and their CT_3, CT_4, *CTSH*.

Table 1. Results for mean and dispersion models of maternal urinary iodine excretion and her thyroid hormones data from gamma fit (using log link).

	Covar.	estimate	s.e.	*t*	P-value
Mean model	Const.	3.08	0.05	66.83	0.00
	MTSH	-0.09	0.01	-8.23	0.00
Dispersion model	Const.	-3.15	0.34	-9.13	0.00
	MT_4	0.08	0.02	3.36	0.00
	MTSH	0.15	0.03	5.19	0.00



(a) (b)

Figure 1. (a) The absolute residual plot with respect to fitted values. (b) The normal probability plot of mean for the non-constant variance models of gamma fit for mothers' urinary iodine excretion for their thyroid hormone data (Table 1).

4.1. Analysis of Maternal Urinary Iodine on Maternal Thyroid Hormones

In this section we analyze the relationship between maternal urinary iodine excretion data (treated as the response variable) and maternal TSH and thyroid hormones (treated as covariates). We use gamma joint generalized linear models, as in (2.2). Note that for these data, the gamma model fit is better than log-normal fit. The selected models have the smallest Akaike information criterion (AICs) value in each class, as AIC selects a model that minimizes the predicted squared error loss.[32,p.203] Results of the analysis are displayed in Table 1.

In Figure 1(a), we plot the absolute values of residuals with respect to fitted values. Figure 1(a) has flat running means, an indication that variance is not increasing with means.[31] In Figure 1(b), we show the normal probability plot for the mean model of our final selected gamma model in Table 1. Figure 1(b) shows no systematic departures, indicating no lack of fit of our final selected models. That there is no missing variable in our fitting is clear from the normal probability plot of the mean model, as there is no gap in this figure. Therefore, the final fitted mean and variance models of the relation of maternal urinary iodine excretion and maternal TSH and thyroid hormones (from Table 1), respectively, are

$$\hat{\mu}_{UIE} = \exp(3.08 - 0.09MTSH) \tag{3.1}$$

and

$$\hat{\sigma}^2_{UIE} = \exp(-3.15 + 0.08\,MT_4 + 0.15MTSH) \tag{3.2}$$

4.2. Analysis of the Relation of Maternal Urinary Iodine to Neonatal Thyroid Hormones

In this section we analyze the relation of maternal urinary iodine excretion (response) data to neonatal TSH and thyroid hormones (covariates). We use gamma joint generalized linear models, as in (2.2). The selected models have the smallest Akaike information criterion (AICs) value in each class. Results of the analysis are presented in Table 2.

In Figure 2(a) and Figure 2(b), we plot, respectively, the absolute values of residuals with respect to fitted values, and the normal probability plot for the mean model of our final selected gamma model in Table 2. Figure 2(a) has flat running means, indicating that the variance is constant under the gamma joint generalized linear model fit. Figure 2(b) presents no lack of fit. Thus, the final fitted mean and variance models of maternal urinary iodine excretion (UIE) on neonatal TSH and thyroid hormones (from Table 2), respectively, are

$$\hat{\mu}_{UIE} = \exp(2.61 + 0.29CT_3 - 0.02CTSH) \tag{3.3}$$

and

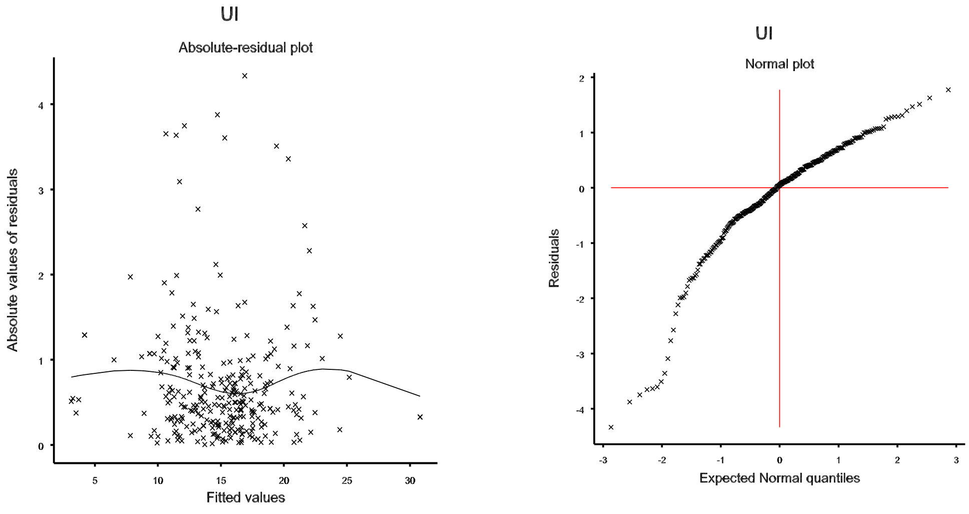
$$\hat{\sigma}^2_{UIE} = \exp(-1.55 - 0.55CT_3 + 0.03CTSH) \tag{3.4}$$

Table 2. Results for mean and dispersion models of maternal urinary iodine excretion on neonatal thyroid hormone data from gamma fit (using log link).

	Covar.	**Estimate**	**s.e.**	***t***	**P-value**
Mean model	Const.	2.61	0.110	23.62	0.00
	CT_3	0.29	0.065	4.39	0.00
	CTSH	-0.02	0.004	-4.59	0.00
Dispers. model	Const.	-1.55	0.314	-4.92	0.00
	CT_3	-0.55	0.214	-2.57	0.01
	CTSH	0.03	0.008	4.00	0.00

4.3. Analysis of Maternal Thyroid Hormone Status

Das and Mukhopadhyay[16] have shown that TSH (*MTSH* and *CTSH*, of the maternal and neonatal groups, respectively) has a negative association with T_3 and T_4. They have not derived the relationship among the thyroid components of mother and neonate. This section presents the relationship between material thyroid hormones, MT_4 and MT_3. We have analyzed the relation of mother $MTSH$ (response) data to that of materianal thyroid hormones MT_3 and MT_4 (covariates). We used log-normal joint generalized linear models, as in (2.1). Here log-normal gives better fit than gamma fit. The selected models have the smallest Akaike information criterion (AICs) value in each class. The results of the analysis are presented in Table 3.



(a)

(b)

Figure 2. (a) The absolute residual plot with respect to fitted values. (b) The normal probability plot of mean for the non-constant variance models of gamma fit for maternal urinary iodine excretion in relation to neonatal thyroid hormone data (Table 2).

Figure 3(a) and Figure 3(b), respectively, display the absolute values of residuals with respect to fitted values, and the normal probability plot for the mean model of our final selected log-normal model in Table 3. Figure 3(a) has flat running means, an indication that variance is constant under log-normal joint generalized linear model fit. Figure 3(b) shows no lack of fit. Thus, the final fitted mean and variance models of maternal $MTSH$ on MT_3 and MT_4 (from Table 3), respectively, are

$$\hat{\mu}_{MTSH} = \exp(2.77 - 0.26MT_3 - 0.12MT_4) \tag{3.5}$$

and

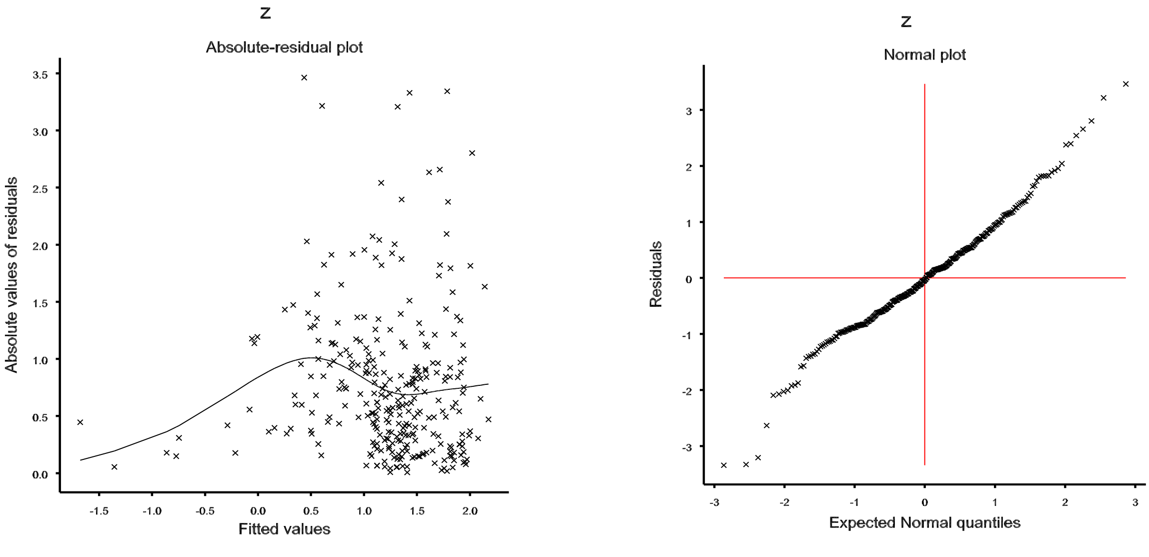
$$\hat{\sigma}^2_{MTSH} = \exp(-3.02 + 0.20MT_4) \tag{3.6}$$

Table 3. Results for mean and dispersion models of maternal thyroid hormone data from log-normal fit.

	Covar.	**estimate**	**s.e.**	***t***	**P-value**
Mean model	Const.	2.77	0.114	24.30	0.00
	MT_3	-0.26	0.106	-2.46	0.01
	MT_4	-0.12	0.014	-8.53	0.00
Dispers. model	Const.	-3.02	0.237	-12.76	0.00
	MT_4	0.20	0.023	8.83	0.00

4.4. Analysis of Neonatal Thyroid Hormone Status

Relationships among the thyroid hormones of neonates are derived here. We analyzed the relation of neonatal *CTSH* (response) data to neonatal thyroid hormones, CT_3 and CT_4, as covariates. We used log-normal joint generalized linear models as in (2.1). Here log-normal gives a better fit than the gamma fit. The selected models have the smallest Akaike information criterion (AICs) value in each class. The results of the analysis are presented in Table 4.



(a) (b)

Figure 3. (a) The absolute residual plot with respect to fitted values. (b) The normal probability plot of the means for the non-constant variance models of log-normal fit for maternal thyroid hormone data (Table 3).

Figure 4(a) displays the absolute values of residuals with respect to fitted values. Figure 4(b) displays the normal probability plot for the mean model of our final selected log-normal model. Figure 4(a) has flat running means, an indication that variance is constant under the log-normal joint generalized linear model fit. Figure 4(b) shows no lack of fit. Thus, the final fitted mean and variance models of neonatal *CTSH* on CT_3 and CT_4 (from Table 4), respectively, are

$$\hat{\mu}_{CTSH} = \exp(4.44 - 0.80CT_3 - 0.18CT_4) \tag{3.7}$$

and

$$\hat{\sigma}^2_{CTSH} = \exp(-1.62 + 0.09CT_4) \tag{3.8}$$

The fitted mean and variance models of neonatal birth weight (y),[16] respectively, are

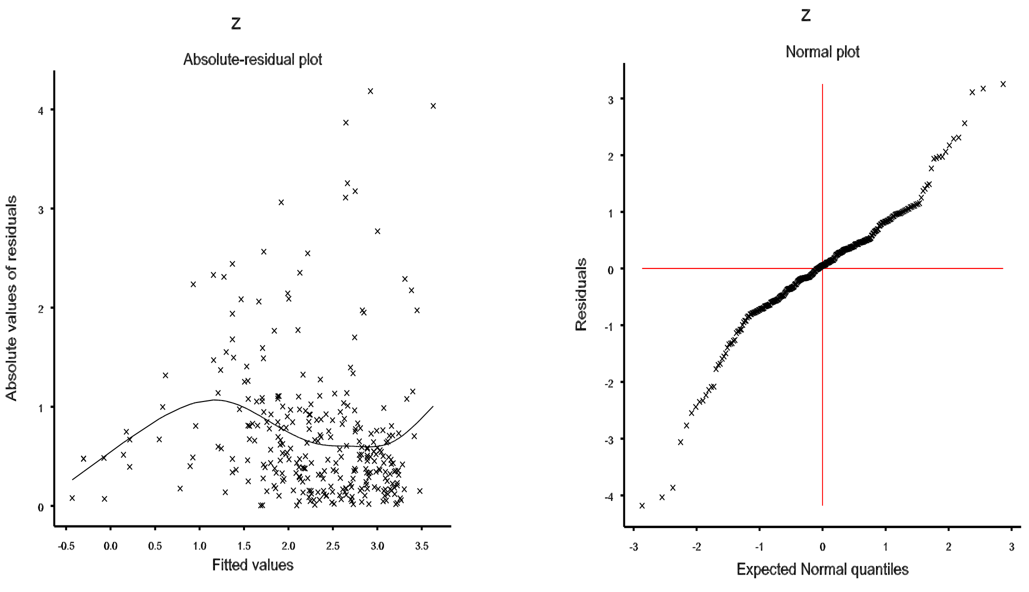
$$\hat{\mu}_Y = \exp(1.261 - 0.003UIE - 0.031MT_3 - 0.004MT_4 - 0.047CT_3 - 0.007CT_4 + 0.001CTSH) \quad (3.9)$$

and

$$\hat{\sigma}^2_Y = \exp(-5.486 + 0.066CT_4) \quad (3.10)$$

Table 4. Results for mean and dispersion models of neonatal thyroid hormone data from log-normal fit.

	Covar.	**estimate**	**s.e.**	***t***	**P-value**
Mean model	Const.	4.44	0.112	39.49	0.00
	CT_3	-0.80	0.124	-6.49	0.00
	CT_4	-0.18	0.018	-9.56	0.00
Dispers. model	Const.	-1.62	0.213	-7.60	0.00
	CT_4	0.09	0.028	3.34	0.00



(a)

(b)

Figure 4. (a) The absolute residual plot with respect to fitted values. (b) The normal probability plot of the mean for the non-constant variance models of log-normal fit for neonate thyroid hormone data (Table 4).

5. Findings, Interpretation, and Discussion

This section presents the findings, interpretation, and discussion of our analysis. The following are the major findings.

(1) Models (3.1) and (3.2), respectively, represent the mean and variance models of estimated maternal urinary iodine excretion on mothers' thyroid hormones. From (3.1) it is seen that the estimated mean of urinary iodine excretion is only explained by the statistically significant effect of maternal TSH (i.e., *MTSH*). It also shows that estimated mean of maternal urinary iodine excretion has

a negative association with *MTSH*. This means that as urinary iodine excretion decreases, *MTSH* tends to increase, and vice versa.

On the other hand, (3.5) represents the mean model of *MTSH*. It shows that *MTSH* has a negative association with both maternal T_3 (or MT_3) and T_4 (or MT_4). This means that if *MTSH* decreases, MT_3 and MT_4 tend to increase, and vice versa. This means that iodine deficiency hypothyroidism of the mother increases her TSH level. Consequently, maternal MT_3 and MT_4 tend to decrease, possibly enough to be diagnosed as hypothyroid. In practice, hypothyroidism (i.e., deficiency of iodine intake) results in an enlarged thyroid gland, known as endemic goiter. This condition is recognized as a significant public health issue.[26] The research literature indicates that cretinism is associated with endemic goiter.[26]

(2) If the mother's iodine intake increases, *MTSH* decreases, and both the MT_3 and MT_4 tend to increase. If the respective decreases and increases reach current laboratory criteria, the condition may be diagnosed as hyperthyroidism. The hyperthyroidism may be associated with maternal autoimmune thyroid disease and possibly papillary cancer.[11]

(3) From (3.2), it is observed that the estimated variance of maternal urinary iodine excretion is positively associated with MT_4 and *MTSH*. This indicates that the variance of the estimated maternal urinary iodine excretion increases if MT_4 or *MTSH* or both increase. Also from (3.5), MT_4 and *MTSH* are negatively associated. This indicates that if MT_4 increases, *MTSH* decreases. We always try to estimate mean urinary iodine excretion with small variance.

(4) In maternal hypothyroidism, *MTSH* increases and MT_4 decreases. The mother's urinary iodine excretion decreases and the variance of iodine excretion increases. In maternal hyperthyroidism, *MTSH* decreases and MT_4 increases. Consequently, the mother's urinary iodine excretion and its variance increase. The estimated variance model (3.2) of maternal urinary iodine excretion does not satisfy the natural relationship of thyroid hormones as in (3.5). This implies that the relationship of iodine to maternal thyroid hormones is complicated, and this suggests that it is important that iodine deficiency corrections be made very accurately.

(5) Models (3.3) and (3.4) represent the mean and variance models of estimated maternal urinary iodine excretion in relation to her neonate's thyroid hormones. In the mean model (3.3), response maternal urinary iodine excretion is associated with the neonate's CT_3 and *CTSH*. The relationships are statistically significant. In the variance model (3.4), estimated variance of maternal urinary iodine excretion is also associated with the neonatal CT_3 and *CTSH*. Again, the relationships are statistically significant. Note that in the models (3.3) and (3.4), response is maternal urinary iodine excretion and explanatory variables are the neonate thyroid hormones. This type of response and covariates are rarely observed in clinical practice.

(6) From (3.3), it is seen that the estimated mean of maternal urinary iodine excretion has a negative association with neonate *CTSH* and a positive association with neonate CT_3. This implies that as maternal urinary iodine excretion decreases, *CTSH* increases and CT_3 decreases, and vice versa. On the other hand, (3.7) represents the mean model of *CTSH*. It shows that CTSH has a negative association with both CT_3 and CT_4. This means that if CTSH increases, CT_3 and CT_4 tend to decrease, and vice versa. This fact supports the model (3.3). Thus, for maternal hypothyroidism due

to iodine deficiency, neonate $CTSH$ increases and CT_3 decreases. Consequently, neonate CT_3 and CT_4 (from model (3.7)) tend to decrease. If the magnitude of these decreases is great enough, the neonate may be diagnosed as hypothyroid. The appropriate conclusion from this is that maternal iodine deficiency may result in hypothyroidism of her neonate. Again, as in serial number 1, it is concluded that iodine deficiency of the mother risks maternal hypothyroidism. Moreover, it also concludes that if the mother suffers from hypothyroidism, her neonate is also at risk of hypothyroidism.

(7) If the mother's iodine intake increases, the increase may be of a magnitude that leads to a diagnosis of hyperthyroidism. Regardless, the increased maternal iodine results in decreased $CTSH$ and increased CT_3. Again from model (3.7), if $CTSH$ decreases, both CT_3 and CT_4 increase. Thus, when the mother is hyperthyroid, her neonate's $CTSH$ decreases and his/her CT_3 and CT_4 increase, possibly leading to neonatal hyperthyroidism. Thus, hyperthyroidism of the mother leads to hyperthyroidism of her neonate (in serial number 2).

(8) From (3.4), it is seen that the estimated variance of maternal urinary iodine excretion has a positive association with neonate $CTSH$ and a negative association with CT_3. This indicates that if the variance increases, $CTSH$ tends to increase and CT_3 tends to decrease, and vise versa. Again from model (3.7), it is seen that if $CTSH$ increases, CT_3 and CT_4 decrease, and vice versa. The model (3.4) supports model (3.7). Thus, the estimated variance of maternal urinary iodine excretion has a natural relationship to neonate thyroid hormone levels. We try to estimate the mean with small variance.

(9) From model (3.9),[16] if maternal urinary iodine excretion is very high (hyperthyroidism), neonate $CTSH$ will be low; consequently, neonatal birth weight will be low, and the neonate may die. On the other hand, maternal hypothyroidism from iodine deficiency results in over weight of the neonate (from model (3.9)) and may result in neonatal obesity. It is well known that obesity of neonates affects their brain development.[28] Screening for congenital hypothyroidism, then, offers a useful index of community iodine nutrition and of the risk of brain damage in developing infants.[27] Thus, the risk of brain damage and neonatal mortality, rather than goiter, have become the main reasons for advocating urgent correction of iodine deficiency. Neonates are more sensitive than children and adults to the effects of iodine deficiency because they have a much smaller intrathyroidal iodine pool with markedly accelerated turnover.

6. Concluding Remarks

This paper focuses on the relationships between maternal urinary iodine and the thyroid status of mothers and their neonates. Chakraborty et al.[25] collected the data set used in this analysis.

Analysis of the data develops some mathematical models. The models show the relationships of maternal urinary iodine excretion to covariables: maternal thyroid status ($MTSH$ and thyroid hormones, MT_3, MT_4); and neonatal thyroid status ($CTSH$ and thyroid hormones, CT_3, CT_4).

The derived models are the relationships of (a) maternal urinary iodine excretion to mother's thyroid hormones; (b) maternal urinary iodine excretion to neonate's CT_3 and CT_4; (c) mother's TSH to MT_3 and MT_4; and (d) neonate's TSH to CT_3 and CT_4. Another model is the relation of neonatal birth weight to the thyroid status of the mothers and their neonates.[16]

The functional relationships (models through (3.1) to (3.10)) are all non-linear. However, standard errors of the estimates (Table 1 to Table 4) are very small, indicating that the estimates are stable.

The analysis in this paper leads to 9 conclusions that are detailed in Section 5. The conclusions are based on the mathematical models (Section 4) of the relationships of maternal urinary iodine excretion to the thyroid status of the mother and her neonate and neonatal weight. The models support most of the facts observed in clinical practice.

The mathematical models in this report show that the relationships of iodine to the thyroid status of mothers and their neonates are not simple. The models reported here illuminate the complex relationships. Fortunately, a true mathematical model can open the truth that is covered by the complex relationships.

Many parameters have been identified in this analysis as statistically significant in mean and variance models; these models can give a clear picture to practitioners of necessary corrections of iodine levels. The corrections are crucial for pregnant women with thyroid disorders to ensure that they have healthy neonates.

This paper does not focus on iodine in relation to diseases such as goiter, brain damage, and papillary cancer. Nonetheless, human beings can potentially benefit from analysis of these relationships through mathematical models. My subsequent paper will focus on the relation of such diseases to iodine status.

As a final note, it is worth emphasizing that neonates have a smaller intrathyroidal iodine pool and more rapid iodine turnover than adults. Because of this, iodine deficiency risks neonatal brain damage and mortality. These, rather than goiter, have become the main reasons for advocating urgent correction of iodine deficiency.

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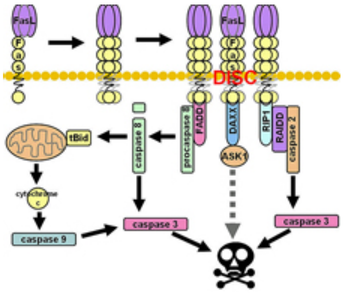

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Clinical Utility of Soluble Fas and Fas Ligand in Thyroid Pathogenesis

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Dhara R. Gajjar,[1] Girish H. Patel,[1] Toral P. Kobawala,[1]
Kamini N. Patel,[1] Urvi B. Parekh,[2] Deepal K. Parekh,[2]
Kirti M. Patel,[3] Shilin N. Shukla,[4] Pankaj M. Shah[5]

[1]Division of Molecular Endocrinology;
[2]Hon. Visiting Physician & Clinical Endocrinologist;
[3]Hon. Deputy Director (Medical), [4]Professor; Medical Oncology;
[5]Hon. Director. The Gujarat Cancer & Research Institute,
NCH Compound, Asarwa, Ahmedabad-380 016, Gujarat, India.

Correspondence: Dr. Girish H. Patel,
Clinical Research Associate: Division of Molecular Endocrinology-I,
& Incharge: Clinical Biochemistry Laboratory,
The Gujarat Cancer & Research Institute,
NCH Compound, Asarwa, Ahmedabad-380 016, India
dharargajjar@gmail.com ghpatel_961@yahoo.co.in

***Abstract.* Background**: The soluble form of Fas (sFas) lacks the transmembrane domain due to alternative splicing. sFas blocks Fas-mediated apoptosis by binding to Fas ligand (FasL). This study was designed to examine whether the apoptotic-inhibitor sFas and the apoptotic inducer FasL are differentially present in two opposite phenotypes of autoimmune thyroid disorders (AITD), nodular goiter (NG), and thyroid cancer. **Methods**: sFas and FasL levels were determined using ELISA in the serum sample of a total 68 patients with Hashimoto's thyroiditis (HT) (n = 15), Graves' disease (GD) (n = 17), nodular goiter (n = 21), and thyroid carcinoma (n = 15). These patients' levels and were compared with 20 age matched, disease-free controls. In addition, for comparison, the levels of thyroglobulin and thyroid peroxidase antibodies were measured. **Results**: All studied groups had raised sFas levels. Levels in AITD patients were statistically significantly higher than in controls. FasL levels were significantly higher in all studied groups except the thyroid cancer group, as compared with controls. Compared to controls, GD patients had higher sFas level, and the HT group had a higher FasL level. Also, compared to controls and the NG group, thyroid cancer patients had higher sFas and lower FasL levels. **Conclusion**: Fas-mediated apoptosis plays an important role in the active stage of the autoimmune process of both GD and HT. Increased sFas in GD and FasL in HT may contribute to homeostasis in the thyroid gland. In thyroid cancer and NG, however, sFas and FasL may provide a key protective signal that helps the cells to avoid apoptosis in a hostile environment.

Keywords Autoimmune thyroid disease • Fas ligand • Graves' disease • Hashimoto's thyroiditis • Nodular goiter • Soluble Fas • Thyroid cancer

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Clinical and Laboratory Studies

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[1]Division of Molecular Endocrinology;
[2]Hon. Visiting Physician & Clinical Endocrinologist;
[3]Hon. Deputy Director (Medical), [4]Professor; Medical Oncology;
[5]Hon. Director. The Gujarat Cancer & Research Institute,
NCH Compound, Asarwa, Ahmedabad-380 016, Gujarat, India.

Corresponding Author: Dr. Girish H. Patel,
Clinical Research Associate: Division of Molecular Endocrinology-I,
& Incharge: Clinical Biochemistry Laboratory,
The Gujarat Cancer & Research Institute,
NCH Compound, Asarwa, Ahmedabad-380 016, India
dharargajjar@gmail.com ghpatel_961@yahoo.co.in

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Introduction

Thyroid problems are among the most common medical conditions, but the development of the conditions is often a slow and insidious process. Patients symptoms often appear gradually and are misunderstand so they are potentially misdiagnosed.[1]

Thyroid disorders including nodular goiter (NG), and cancer of thyroid epithelial origin as well as autoimmune thyroid diseases (AITD) such as Hashimoto's thyroiditis (HT) and Graves' diseases (GD) are well known. Studies indicated they these thyroid disorders may be associated with dysregulation of the apoptotic signaling pathway.

The processes involved in apoptosis are tightly regulated. Alterations in their functioning may result in disorders such as autoimmune diseases and cancer.[2,3] Apoptosis may play an important role in the homeostasis of thyroid follicular cells as well as destructive mechanisms in thyroid disease.

Apoptosis is a mechanism by which cytotoxic T lymphocytes can destroy thyrocytes in thyroiditis, leading in turn to hypothyroidism.[4,5] In contrast, the suppression of apoptosis may contribute to proliferative diseases of the thyroid gland, such as goiter, cancer, and GD.[5,6]

However, little is known about the mechanisms and regulation of apoptotic signaling in thyroid cells. It is important to define the signaling components of apoptosis in thyroid follicular cells. These signaling components may help in providing insights into potential pathogenic mechanism and lead to development of pharmacological interventions for the treatment of thyroid disease.[7]

The apoptotic mechanism of a cell involves several components: death receptor, adaptor molecules, the caspase cascade, mitochondria, and the Bcl-2 proteins.[8,9]

The death receptors known today belong to the tumor necrosis factor receptor (TNFR) gene superfamily which is defined by similar, cysteine-rich extra cellular domains. The death receptors, which form a subgroup of the superfamily TNFR, are composed of three domains: an extracellular domain, a transmembrane domain, and a cytoplasmic domain. The cytoplasmic domain contains a homologous domain of 80 amino acids termed the "death domain." The death domain (DD) bridges the death receptors with the apoptotic machinery or some adaptor molecules that transmit apoptotic signals from death receptors that themselves contain death domains.[10,11]

One of the best characterized death receptors is Fas known as CD95/APO-1/TNFRSF6. It is a 36 KDa cell surface type-1 membrane glycoprotein. Fas ligand (FasL) is a type-II transmembrane protein of the same family, which has the ability to bind Fas.[12] Fas has been shown to be an important mediator of apoptotic cell death. It is also involved in inflammation. Binding of FasL induces trimerization of Fas in the target cell membrane. Activation of Fas causes the recruitment of Fas associated protein with death domain (FADD) via interactions between the death domain of Fas and FADD. Procaspase-8 binds to Fas-bound FADD via interactions between the death effecter domain (DED) of FADD. Procaspase-8 then leads to the activation of caspase-8. Activated caspase-8 cleaves (activates) other procaspases, in effect beginning a caspase cascade that ultimately leads to apoptosis.

Fas can occur both as a cell surface protein and a soluble protein. Cell surface Fas is anchored by a single membrane-spanning domain and is widely expressed in normal and malignant cells.[13] Soluble Fas (sFas), alternatively spliced Fas mRNA that results from deletion of exons 3, 4, 6 & 7 and lacks 21 amino acid residues that contain a transmembrane domain. sFas protects target cells from Fas-induced apoptosis by competitively binding with FasL and altering lymphocyte development and proliferation in response to self antigens.[14]

The Fas pathway has been demonstrated to be the important apoptotic pathway in the thyroid gland. Its role in the pathogenesis of thyroid diseases, however, is controversial and a subject of much debate.[16] Regulation or modulation of this pathway can occur at multiple levels throughout the pathway. This may include changes in the level of the expression of Fas or its ligand;[12,17,18,20] regulation of components of intracellular signaling;[9,22,23,24] and expression of proteins that promote survival, such as members of the Bcl-2 gene family.[3,9,23,26,27]

This study summarizes the role of Fas-mediated apoptosis in thyroid diseases such as goiter, thyroid cancer, and autoimmune thyroid diseases. In addition, markers of humoral immune response (thyroglobulin and thyroid peroxidase antibodies) were also evaluated to compare with sFas and FasL levels.

Materials and Method

Patients and Sample Collection. A total of 68 patients with thyroid disorder (age range: 07-to-78 years) were enrolled in the current study. All the patients were newly diagnosed and untreated for their condition at the time of blood collection. Also, due and required consent was taken from each patient to enroll in this study prior to blood collection.

The study was approved by Institutional Scientific Review Board & Ethics Committee. The diagnosis of GD and HT was based on commonly accepted clinical and laboratory criteria. In case of NG and thyroid cancer, blood samples collected prior to surgery and diagnosis was based on histopathological investigation. Of all 68 patients, thirty two (47.1%) had AITD, twenty (30.9%) had NG, and fifteen (22.1%) had thyroid carcinoma.

For comparison with patients, 20 age matched, healthy individuals were included. They had normal thyroid function test results, no goiter, and were negative for antithyriod autoantibodies.

Venous blood samples were collected in Vacutainer tubes between 9:00 to 11:00 am. The samples were allowed to clot for 30 minutes at room temperature. Sera were obtained by centrifugation, were aliquoted, and stored at -20ºC till analysis. All the samples were analyzed for thyroid hormone levels and thyroid autoantibodies.

Evaluation of Soluble Fas and Fas Ligand. Circulating sFas and FasL were estimated using sandwich ELISA (Quantikine, R&D systems, USA) kits. Sample activation and dilution were performed according to the manufacturer's protocol. The unit of measure for the levels of sFas and FasL was ng/mL. The detection range was 0-2.0 ng/mL and 0-1.0 ng/mL for sFas and FasL, respectively. All enzymatic reaction products were determined photometrically at 450 nm by Plate reader (Thermolabsystems, Finland; Multiskan spectrum).

Evaluation of Thyroid Autoantibodies. Commercially available kits (Immunotech, France) were used for the measurement of serum anti-thyroglobulin (anti-TG), and anti-thyroid peroxidase (anti-TPO) antibodies with the automated gamma counter (Packard, cobra). The detection range was 0-to-250.0 ng /mL and 0-2100.0 IU /mL for TG and TPO, respectively. Measurements were based on radioimmunoassay and immunoradiomatric assay.

Statistical Analysis. All the statistical analysis carried out with the SPSS 17.0 software and statistical significance was computed using students' *t*-test and anova. Receiver's operating characteristic (ROC) curve was also constructed to determine the discriminating efficacy of sFas and FasL. $p < 0.05$ was considered as a statistically significant. The correlation of TPO and TG with sFas and FasL was done by parametric analysis, i.e. Pearson's correlation and non-parametric, i.e. Spearman's correlation test.

Results

A total of 68 samples and 20 controls were analyzed for sFas and FasL levels. Higher mean levels of sFas and FasL observed in thyroid diseases were statistically significant when compared with controls. The results of circulating serum sFas and FasL levels in the examined thyroid disease patients are shown in Table-1 and 2 as mean ± standard error of the mean in ng/mL.

Levels of sFas were higher in all the studied groups as compared to the controls. However, the highly significant values were found in GD patients as compared to controls (0.791 ± 0.060 vs 0.566 ± 0.012, p = 0.0001) and compared to HT (0.791 ± 0.060 vs 0.645 ± 0.045, p = 0.068). Higher levels in HT (0.645 ± 0.045, p = 0.065) and thyroid cancer patients (0.734 ± 0.102, p = 0.069) were close to statistically significant. There was also a difference between thyroid cancer patients and NG (0.734 ± 0.102 vs 0.599 ± 0.033, p=0.164).

Table-1. Significance of Soluble Fas levels in patients with various thyroid diseases as compared to controls.

Subjects	N	Soluble Fas			
		Mean ± S.E. *(ng/mL)*	Minimum	Maximum	*p* value
Controls	20	0.566 ± 0.012	0.430	0.680	
Total patients	68	0.687 ± 0.031	0.340	2.000	0.042
Autoimmune thyroid disease	32	0.723 ± 0.040	0.400	1.500	0.004
Graves' disease	17	0.791 ± 0.060	0.530	1.500	0.0001
Hashimoto's thyroiditis	15	0.645 ± 0.045	0.400	1.050	0.065
Nodular goiter	21	0.599 ± 0.033	0.340	0.960	0.37
Thyroid cancer	15	0.734 ± 0.102	0.390	2.000	0.069

As Table-2 shows, compared to controls, the mean level of Fas ligand was significantly higher in all patient groups except thyroid cancer patients. The difference in FasL levels between GD (0.056 ± 0.003) and HT (0.062 ± 0.007) was not significant. Significantly higher levels of FasL were observed for NG patients compared to controls (0.062 ± 0.006 vs 0.035 ± 0.005, p = 0.003) and compared to thyroid cancer patients (0.062 ± 0.006 vs 0.042 ± 0.004, p = 0.028).

Table-2. Significance of Fas ligand levels in patients with various thyroid diseases as compared to controls.

Subjects	N	**Fas Ligand**			
		Mean ± S.E. *(ng/mL)*	Minimum	Maximum	*p* value
Controls	20	0.035 ± 0.005	0.005	0.064	
Total patients	68	0.056 ± 0.003	0.006	0.0154	0.001
Autoimmune thyroid disease	32	0.059 ± 0.003	0.025	0.110	0.0001
Graves' disease	17	0.056 ± 0.003	0.035	0.084	0.002
Hashimoto's thyroiditis	15	0.062 ± 0.007	0.025	0.110	0.003
Nodular goiter	21	0.062 ± 0.006	0.015	0.154	0.003
Thyroid cancer	15	0.042 ± 0.004	0.006	0.008	0.35

Levels of TPO and TG antibodies were also measured and found higher in all groups except TG in the HT group (Table-3). Parametric and nonparametric correlation tests showed significant linear correlations between sFas and TG ($r = 0.319$, $p = 0.05$), TPO ($r = 0.384$, $p = 0.019$). Significant linear correlations were also found between sFas and TPO antibodies ($r = 0.590$, $p = 0.021$) in HT patients and between sFas and TG ($r = 0.543$, $p = 0.011$) in NG patients. There was no correlation between FasL and TG or TPO antibodies.

ROC curve indicates that both sFas and FasL

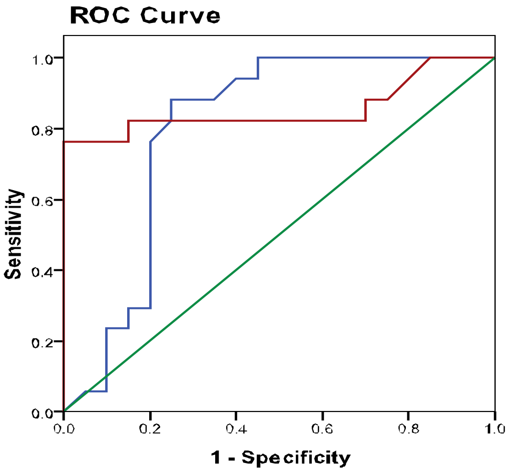
Table-3. Levels of thyroid peroxidase and thyroglobulin in patients with various thyroid diseases and controls.

Subjects	N	**Thyroid peroxidase**		**Thyroglobulin**	
		Mean ± S.E. *(IU/mL)*	*p* value	Mean ± S.E. *(ng /mL)*	*p* value
Controls	20	20.16 ± 6.63		6.16 ± 0.92	
Total patients	68	781.99 ± 172.86	0.02	56.90 ± 15.45	0.08
Autoimmune thyroid disease	32	1236.01 ± 306.12	0.003	48.56 ± 18.30	0.074
Graves' disease	17	1198.90 ± 390.55	0.002	84.47 ± 32.20	0.012
Hashimoto's thyroiditis	15	1278.07 ± 494.86	0.006	7.85 ± 4.21	0.65
Nodular goiter	21	598.50 ± 256.23	0.034	57.98 ± 33.07	0.13
Thyroid cancer	15	70.30 ± 57.59	0.32	73.19 ± 37.12	0.044

ROC curve indicates that both sFas and FasL exhibited a good discriminatory efficacy between controls and GD patients (sFas: AUC-0.856; FasL: AUC-0.801) (Figure-1).

Figure-1. ROC curve for Soluble Fas (red line) and Fas ligand (blue line) between graves's disease patients with controls.

Variable	**Area under the curve**	***p* value**	**95% CI**	
			Lower	Upper
Soluble Fas	0.856	0.0001	0.712	1.000
Fas ligand	0.801	0.002	0.647	0.956



Diagonal segments are produced by ties.

Discussion

The control of thyroid gland volume results from an equilibrium between the trophic action of TSH and thyrocyte apoptosis. Apoptosis is limited to some extent by resistance to Fas activation by producion of an inhibitor of apoptotic signal transduction.[24] In the Fas/FasL apoptotic pathway, Fas, FasL and sFasL are thought to induce apoptosis while sFas inhibits apotosis.

The current prospective study was designed to examine whether sFas, an inhibitor of apoptosis, and FasL, an inducer of apoptosis are differentially present in two opposite phenotypes of autoimmune thyroid disorders, nodular goiter, and thyroid cancer.

In the study, all patients with various thyroid diseases showed elevated levels of sFas. However, the highest concentrations were found in patients with AITD. Hiromatsu et al. demonstrated Fas expressed in cell membranes and predisposed to FasL mediated apoptosis. Fas may be present both on the thyrocytes of patients with AITD with infiltrating lymphocytes. Thus, Fas/FasL interaction considerably influences destruction of thyroid tissue on one side and plays an important part in the elimination of autoreactive lymphocytes on the other side.[25]

Moreover, we found higher levels of sFas in GD patients. This finding concurs with the study result of Shimoka et al.[26] and Hiromatsu et al.[27] They have demonstrated that increased sFas in GD suggest increased expression of an alternatively spliced mRNA variants that produces sFas proteins that decreases the cell expression of Fas and may induce thyroid cell growth and production of TSH receptor antibodies by protecting against apoptosis of thyroid cells.

Fountolakis et al. have also demonstrated that elevated sFas in GD may reflect reduced full length membrane Fas and may have a role in the inhibition of Fas-mediated apoptosis of thyrocytes in this condition.[28] Circulating forms of Fas are commonly considered as a factor that inhibits membrane Fas-mediated apoptosis. These originate from both proteolytic cleavage from the transmembrane domain and direct mRNA transcription.[23] In our study, circulating sFas levels were simultaneously increased with TG and TPO antibodies in GD. Thus, sFas may play a role with these molecules in preventing the Fas/FasL-mediated apoptosis of thyrocytes in GD. The local production of sFas by thyrocytes, its regulation by cytokines, and its increased serum levels in GD have been confirmed. These studies suggest that sFas, by interfering with the Fas-FasL interaction, plays a role in the pathogenesis of GD.[26,27]

Our data have shown elevated levels of Fas ligand in HT compare to healthy individuals and GD patients. In contrast, sFas was decreased in HT compare to GD. An increase in sFas concentration especially in patients with HT compare to healthy individuals may be a consequence of the enhanced releasing of circulating forms of Fas that seem to reflect the intensity of Fas/FasL mediated apoptosis. Recent studies have revealed that FasL is also expressed in immune-privileged sites, such as the retina[29] and testis.[30]

Hiromatsu et al. has shown that in HT, a higher degree of apoptosis is more due to thyrocytes with a more intense Fas expression on follicular cells than infiltrating lymphocytes.[25] The presence of apoptosis has also been reported in HT.[4] Recently, Giordano et al. reported the constitutive expression of FasL in normal and HT thyrocytes, indicating that they contribute to the development of clinical hypothyroidism.[31] FasL was initially reported to be expressed in activated T cells and NK cells.[16] Moreover, taking into account the high cytotoxic capacity of a TPO antibodies, a positive correlation between sFas and TPO antibodies in HT patients suggest that increased sFas may reflect the intensity of the immune-involved destruction of the thyroid follicular cells.

Andrikoula et al. concluded that increased sFas in multinodular goiter may indicate an increased expression of alternatively spliced Fas mRNA variants and decreased expression of cell surface protein. This may enhance thyroid cell proliferation by protecting thyroid cells from Fas-mediated apoptosis.[32] A similar observation was seen in our study. This indicates that sFas can play a vital role in the pathogenesis of NG. sFas simultaneously increases with TG antibodies in patients with goiter, showing unbalanced apoptosis and increased thyroid cell proliferation.

The functions of Fas have not yet been fully elucidated, but there are several investigations suggesting roles of both sFas and FasL in cancer progression. More recently, it has been reported that some tumor cells, including those of epithelial origin, express FasL.[33,34] Several studies have demonstrated high concentration of soluble Fas in large tumors in patients with ovarian cancer, cancer of the corpus uteri, colorectal cancer, thyroid cancer and adenoma, and adrenocortical cancer.[35] Using immunohistochemistry and mRNA studies, Basolo et al. demonstrated that different thyroid tissue expressions of Fas and FasL are simultaniously upregulated in adenomas and in well-differentiated papillary and follicular carcinomas. In contrast, Fas is suppressed, and FasL is strongly reduced in the most aggressive histological variants.[36] In our study, we observed that thyroid cancer patients had higher levels of sFas in lower levels FasL than patients with NG and AITD.

Summary

In summary, our study demonstrate that circulating sFas and FasL concentrations are increased in patients with AITD, especially those with GD. This indicates enhanced thyroid cell proliferation by protecting against thyroid cell from Fas-mediated apoptosis. However, in contrast to GD, decreased sFas in HT increased FasL, indicate destruction of thyrocytes. In cases of thyroid cancer and NG, sFas may provide a key protective signal that helps the cells to avoid apoptosis in a hostile environment. Further studies with larger numbers of patients that evaluate the post-therapeutic changes in the levels of these molecules may provide additional predictive value in disease differentiation and pathogenesis.

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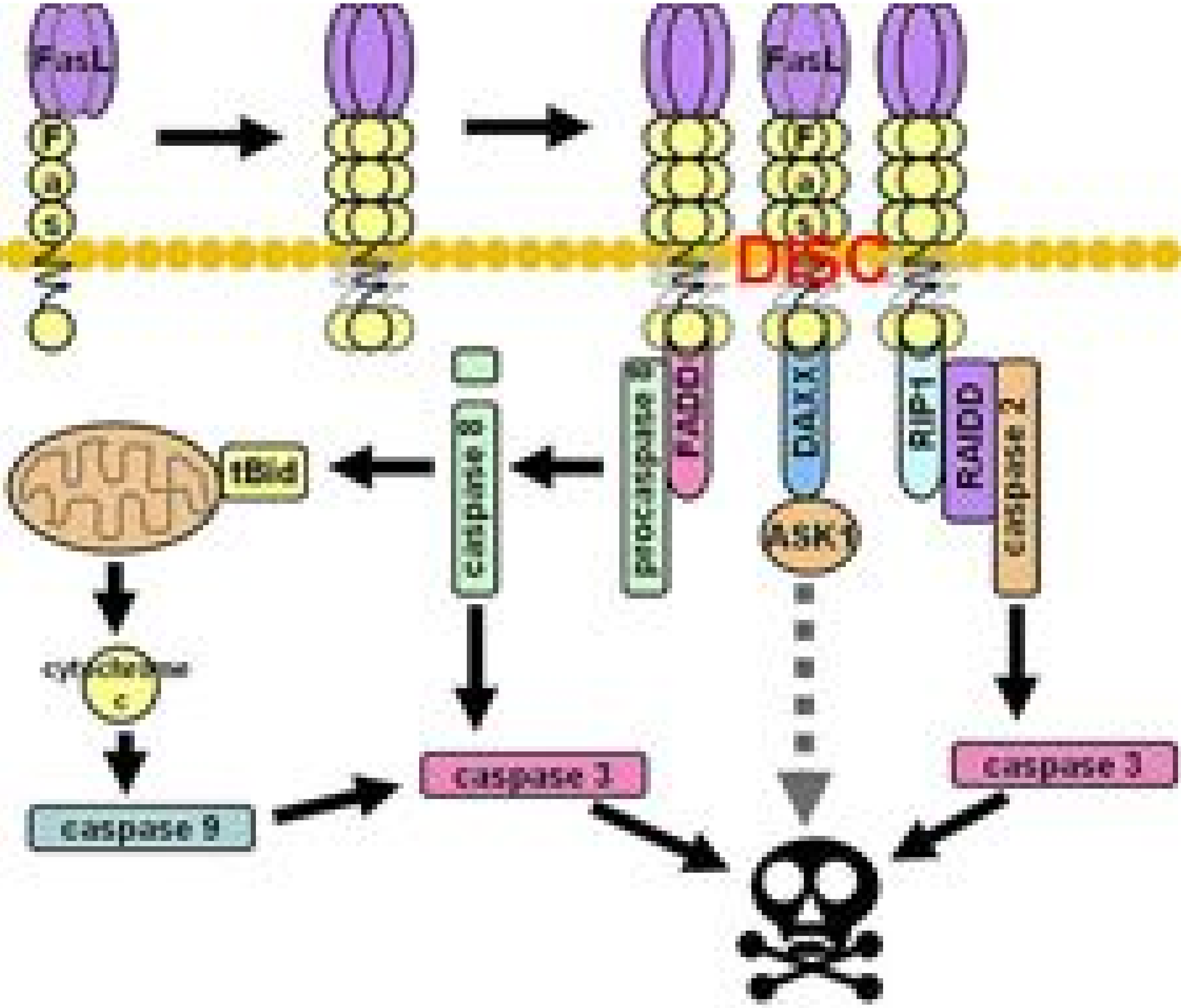
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Clinical Utility of Thyroperoxidase Antibody Testing in Patients with Pulmonary Hypertension

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Justin J. Gisel, MD, John T. Daniels, DO, and Charles D. Burger, MD*

Department of Pulmonary and Critical Care, Mayo Clinic Jacksonville

**Correspondence*: Charles D. Burger, MD, Pulmonary and Critical Care Division,
Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224
Ph: 904-953-2000 Fax: 904-953-2082 burger.charles@mayo.edu

Abstract. Background: The association of autoimmune thyroid disease (AITD) in patients with pulmonary arterial hypertension (PAH) has been well-recognized, yet the best method to screen for thyroid disease is unclear. Since there may be an underlying common immunopathologic link, we sought to determine whether testing for thyroperoxidase antibody (TPOAb) would be a useful screening tool for AITD in PAH. **Methods**: This retrospective study comprised 101 consecutive PAH patients seen at Mayo Clinic Jacksonville's Pulmonary Hypertension Center from 2001 to 2008 who fulfilled two requirements: they met the WHO criteria for PAH, and they had measurements of TPOAb levels and thyroid stimulating hormone (TSH). **Results**: Of the 101 patients in the cohort, 37 met criteria for AITD. Two patients had an elevated level of TPOAb in the setting of a normal TSH and not taking thyroid hormone medication. TPOAb sensitivity was 46% (95% confidence interval [CI], 29 to 63%), specificity 97% (95% CI 89 to 99%), positive predictive value (PPV) was 89% (95% CI 67 to 98%), and negative predictive value (NPV) was 76%(95% CI 65 to 84%). **Conclusions**: Many patients with PAH have a concomitant thyroid disorder. Screening for TPOAb revealed elevated levels in approximately half of those with AITD and PAH. However, TPOAb was elevated in only 2 patients with both a normal TSH and no prior diagnosis of thyroid disease. The low sensitivity of TPOAb demonstrates limited value as a screening test for thyroid disease compared to a medical history and a
measurement of TSH.

Keywords. Thyroperoxidase • Antibody • Pulmonary hypertension • Thyroid • Autoimmune

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Justin J. Gisel, MD, John T. Daniels, DO, and Charles D. Burger, MD

Department of Pulmonary and Critical Care, Mayo Clinic Jacksonville

Correspondence: Charles D. Burger, MD, Pulmonary and Critical Care Division,
Mayo Clinic Jacksonville, 4500 San Pablo Road, Jacksonville, FL 32224
Ph: 904-953-2000 Fax: 904-953-2082 burger.charles@mayo.edu

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Introduction

Thyroid thyroperoxidase antibodies (TPOAb) are circulating immunoglobulins directed against a component of the smooth endoplasmic reticulum of thyroid cells.[1] Detectable levels of TPOAbs are mainly associated with thyroid autoimmune disorders and thyroid cancers. However, a greater frequency of elevated levels has been found in a host of other systemic diseases. The diseases include rheumatoid arthritis, myasthenia gravis, diabetes mellitus, systemic lupus erythematosus, biliary cirrhosis, mixed connective tissue disease, Sjögren's syndrome, Addison's disease, and pernicious anemia.[2,3,4,5,6] To date, no direct pathological role has been definitively determined for this antibody; however, TPOAb has been used as a marker for autoimmune thyroid disease.[7,8]

Pulmonary hypertension is a progressive disease characterized by dyspnea, exercise limitation, and chest discomfort, often leading to right heart failure and death.[9,10] In an attempt to organize pulmonary hypertension, the World Health Organization (WHO) has classified pulmonary hypertension into five general groups.[11] An adaptation of the current WHO classification is shown in Table 1.[11] Pulmonary arterial hypertension (WHO Group 1) contains a number of subsets into which thyroid disorders have been included.[11] Indeed, thyroid disease has been associated with pulmonary hypertension for two decades.[12,13,14,15,16,17,18]

Current recommendations acknowledging an association between thyroid disease and pulmonary hypertension describe the need for further research, as it remains unclear whether or not thyroid disease is causally related to pulmonary arterial hypertension.[19] One prior publication advocated a systematic, comprehensive evaluation for thyroid disease in all patients with pulmonary arterial hypertension utilizing clinical, biochemical, and serologic parameters

Table 1. The Revised World Health Organization Classification of Pulmonary Hypertension*

Group 1. Pulmonary arterial hypertension
- Idiopathic
- Familial
  - Related conditions: collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infection, drugs and toxins, thyroid disorders, myeloproliferative disorders, splenectomy, hemoglobinopathies, glycogen storage disease
- Associated with significant venous or capillary involvement
- Persistent pulmonary hypertension of the newborn

Group II. Pulmonary venous hypertension
- Left-sided atrial or ventricular heart disease
- Left-sided valvular heart disease

Group III. Pulmonary hypertension associated with hypoxemia
- Chronic obstructive pulmonary disease
- Interstitial lung disease
- Sleep-disordered breathing
- Alveolar hypoventilation disorders
- Chronic exposure to high altitude
- Developmental abnormalities

Group IV. Pulmonary hypertension due to chronic thrombotic disease, embolic disease, or both
- Thromboembolic obstruction of proximal pulmonary arteries
- Thromboembolic obstruction of distal pulmonary arteries
- Pulmonary embolism

Group V. Miscellaneous
- Sarcoidosis, pulmonary Langerhan's-cell histiocytosis, lymphangiomatosis, compression of pulmonary vessels

*The table has been adapted from Simonneau et al.[11]

of autoimmune thyroid disease.[20] Recognizing the correlation between autoimmune thyroid disease and pulmonary arterial hypertension, we postulated that screening for TPOAb would help to determine whether pulmonary arterial hypertension is associated with thyroid disease.

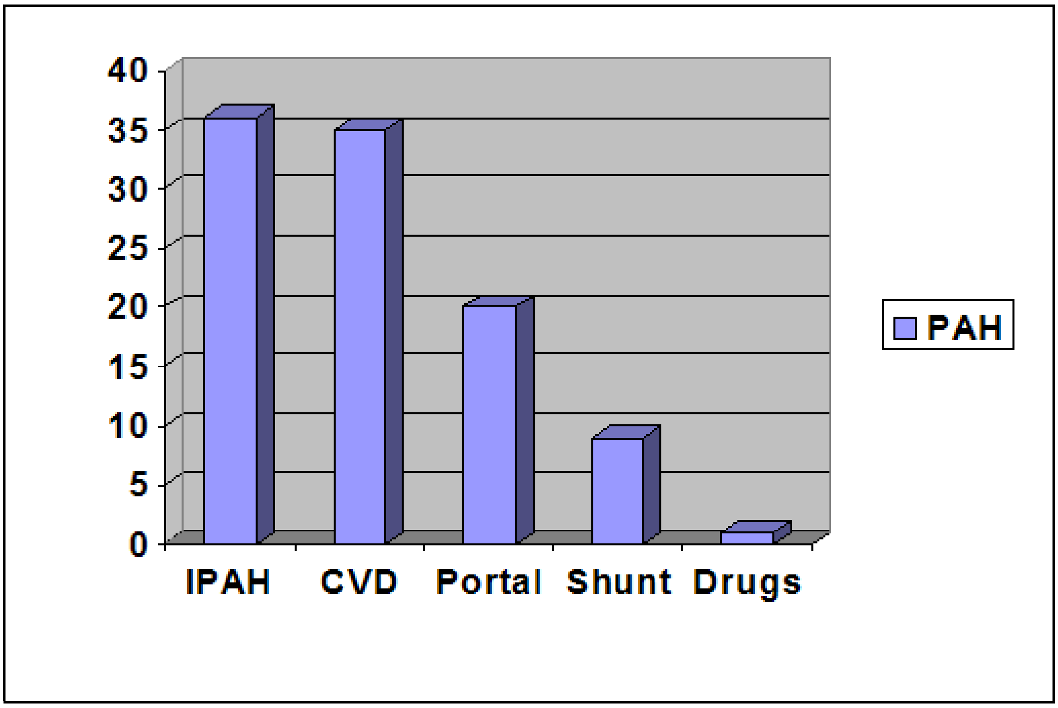
Materials and Methods

Patients. This study was approved by the Mayo Clinic Institutional Review Board. Consecutive patients with pulmonary arterial hypertension seen at Mayo Clinic Jacksonville Pulmonary Hypertension Center from 2001 to 2008 were studied retrospectively.

Data Collection. The following information was collected for the patients in this observational study: age, sex, pulmonary hypertension characteristics, and thyroid function test results. Pulmonary hypertension was defined as sustained mean pulmonary artery pressure >25 mm Hg at rest or systolic pulmonary arterial pressure >35 mm Hg. The diagnosis was confirmed by history, physical examination, echocardiography, right heart catheterization, and comorbid conditions.

Pulmonary venous hypertension was excluded by a pulmonary artery occlusion pressure ≤15 mm Hg. Information about the etiology of the patient's pulmonary arterial hypertension is shown in Figure 1. The mean pulmonary artery pressure in this cohort was 44 ± 14 mm Hg. Four patients were diagnosed with pulmonary arterial hypertension based on echocardiographic right ventricular systolic pressure >35 mmHg and had no reported mean pulmonary artery pressure.

Thyroid disease was determined by an abnormal thyroid function test result, or by a previous diagnosis of thyroid disease and the current use of thyroid replacement therapy. Hypothyroidism was defined by TSH levels >5.5 mIU/L (Hypersensitive Enzyme Immunoassay on Beckman Coulter DXI; reference range, 0.1 to 5.5 mIU/L); free thyroxine levels <0.8 ng/dL (immunoradiometric assay on Beckman Coul-



IPAH (Idiopathic Pulmonary Arterial Hypertension); CVD (Collagen vascular disease); Portal (Portal hypertension); Shunt (Congenital systemic-to-pulmonary shunts).

Coulter DXI; reference range, 0.8 to 1.4 ng/dL); or a history of thyroid disease treated with thyroid hormone replacement. Hyperthyroidism was defined by a TSH level < 0.1 mIU/L or a free thyroxine level > 1.4 ng/dL and no current use of thyroid hormone replacement. Autoimmune thyroid disease was defined as any of the aforementioned including an abnormal TPOAb level >20 IU/mL (reference value ≤ 20 IU/ml).

Statistical Analysis. Sensitivity, specificity, positive predictive value, and negative predictive value were determined for TPOAb measurements in the setting of thyroid disease as defined above utilizing the standard formulas.

Results

Of the 101 patients included in the study, 74 were female. Ages of the cohort ranged from 21 to 88 years, and the mean age was 62 years. Two patients were on continuous IV epoprostenol prior to evaluation. Thirty-seven of the study patients (37%) were found to have autoimmune thyroid disease.

Overall, 17 patients were positive for TPOAb, 15 patients were found to have an abnormal TSH levels, and 17 patients had a previous history of thyroid disease and were on thyroid hormone replacement. Of those with autoimmune thyroid disease, 32 were diagnosed with hypothyroidism, and 2 were diagnosed with hyperthyroidism. Two had abnormal TPO-Ab levels with normal TSH values and were not on thyroid hormone replacement.

The sensitivity of TPOAb testing in the setting of thyroid disease associated pulmonary arterial hypertension was 46% (CI 29 to 63%). The specificity was 97% (CI 89 to 99%), positive predictive value 89% (67 to 98%), and negative predictive value 76% (CI 65 to 84%). Of those with autoimmune thyroid disease, only 2 had elevated levels of TPOAb with a reference range TSH and an absence of thyroid hormone replacement.

Discussion/Conclusion

Our data indicate a incidence of thyroid disease in pulmonary hypertension (37%) similar to that reported in previous studies.[20,21,22] Other researchers have reported an incidence as high as 49%.[20] Due to the strong association of the two conditions, it may be reasonable to screen patients with pulmonary hypertension for the possibility of underlying autoimmune thyroid disease. It is not clear, however, which test is most effective for screening.

The issue of how the screening should take place has been left open ended. This has resulted from the lack of a clear understanding of the association between pulmonary hypertension and autoimmune thyroid disease and the need for further evaluation of that association.

In recent studies, researchers have speculated on a common, underlying etiological link between the two conditions.[20,23,24] Possible associations include an as yet undiscovered immunogenetic overlap/ susceptibility, prostacyclin therapy, or an inflammatory process.[20,25,26]

TPOAb levels were abnormal in 17% of our population with autoimmune thyroid disease and pulmonary arterial hypertension. However, the elevated TPOAb levels added little-to-no value as compared to a TSH, a history of thyroid disease, and the current use of thyroid hormone replacement.

This low sensitivity of TPOAb demonstrates limited usefulness as a screening test for thyroid disease in pulmonary hypertension. In only two clinical cases were the TPOAb levels felt to be additive in this cohort of 101 patients. Neither of these cases involved underlying immunological disease or ongoing prostacyclin therapy; instead, they involved portal hypertension and end-stage liver disease due to Hepatitis C. In addition, both had failed treatment with alpha-interferon in the past prior to their evaluation. Incidences of autoimmunity developing after alpha-interferon as well as thyroid abnormalities in chronic viral hepatitis are well described in the literature and may account for this finding.[24,26,27]

Summary

This study reinforces the association between autoimmune thyroid disease and pulmonary arterial hypertension. However, we found testing for TPOAb to have low sensitivity. This makes it a poor screening test and an unlikely player in the future search for a common immunogenetic susceptibility.

While the majority of abnormal TPOAb levels were found in patients with thyroid disease, two cases represented patients having portal hypertension with end-stage liver disease secondary to hepatitis C; both patients had undergone alpha-interferon in the past. A TSH and history were adequate in evaluating the possibility of thyroid dysfunction in patients with pulmonary arterial hypertension.

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Lower Resting Metabolic Rate and Basal Body Temperature of Fibromyalgia Patients Compared to Matched Healthy Controls

(Full Text Free in pdf format)

John C. Lowe,[Δλ] G. Honeyman,[Δ] Jackie Yellin[Δ]

[Δ]Fibromyalgia Research Foundation, Houston, Texas, U.S.A.

[λ]*Contact:* Dr. John C. Lowe, drlowe@drlowe.com, drlowe@FibromyalgiaResearch.org

ABSTRACT. ***Introduction***. All symptoms and most objectively verified abnormalities of fibromyalgia are common among patients with hypothyroidism or partial peripheral thyroid hormone resistance. In treatment trials, thyroid hormone therapy has reduced or eliminated fibromyalgia symptoms, and a long-term follow-up study showed that improvement with thyroid hormone therapy lasted 1-to-5 years. In a previous study by the authors, solicited female fibromyalgia patients had significantly lower resting metabolic rates and basal body temperatures than matched healthy controls. In this study, the resting metabolic rates and body temperatures of fibromyalgia patients previously evaluated at a specialty metabolic clinic were compared with healthy controls to whom they were matched.

Methods. Fifteen female fibromyalgia patients and 15 healthy females served as study subjects. Patients were clinical cases selected to match controls by sex, age, weight, and activity level. Resting metabolic rate (RMR) was measured by indirect calorimetry (MedGem®), basal body temperature with digital thermometers, and body composition by bioelectrical impedance. The mean measured resting metabolic rate (mRMR) was compared to percentages of the mean predicted RMR (pRMR) by two methods: fat-free weight (Sterling-Passmore equation: SP) and sex, age, height, and weight (Harris-Benedict and Mifflin-St. Joer equations: HB and MSt.J). Measurements were taken during the follicular phase of subjects' menstrual cycles.

Results. Patients had a lower mean mRMR (939.70 ± 216.04 kcal/d vs 1293.40 ± 166.34 kcal/d, $p = 0.00001$) and lower mRMRs as percentages of pRMRs (SP: -26.91 ± 13.36% vs -6.826 ± 12.55%, $p < 0.0001$. HB: -32.45 ± 13.48% vs -9.13 ± 9.51%, $p = 0.0001$; MSt.J: -27.96 ± 14.53% vs -5.089 ± 11.30%, $p = 0.0002$). Age and fat-free weight accounted for 62% of variability in controls'mRMRs. Fat-free weight, water as a percentage of body weight, and fibromyalgia symptom intensity accounted for 83% of the variability of patients' mRMRs. Patients' mean basal body temperature was significantly lower than that of controls (96.38 ± 0.98 F vs 97.54 ± 0.59 F, $p = 0.001$). Patients' serum free T3 level was significantly lower than that of controls (3.18 ± 0.559 vs 3.75 ± 0.717 pg/mL, $p = 0.023$).

Conclusions. The patient group had a lower mean mRMR and lower mRMR as percentages of pRMRs. Patients also had a significantly lower mean basal body temperature. Neither calorie restriction nor low fat-free weight accounted for patients' lower RMRs. As in the previous study, fibromyalgia patients' normal fat-free weight argues against low physical activity with poor physical fitness as the mechanism of their low RMRs. Free T4, free T3, and TSH levels did not correlate with fibromyalgia measures or RMRs in either patient or control group. The lack of correlation does not rule out inadequate thyroid hormone regulation as the mechanism of the low RMRs because studies have not shown that these laboratory values reliably predict RMR values.

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Lower Resting Metabolic Rate and Basal Body Temperature of Fibromyalgia Patients Compared to Matched Healthy Controls

John C. Lowe,[Δγ] **Gina Honeyman,**[Δ] **Jackie Yellin**[Δ]

[Δ]Fibromyalgia Research Foundation, Boulder, Colorado, U.S.A.

[γ]Contact: Dr. John C. Lowe, 1007 Pearl Street, Suite 280, Boulder, CO, 80302, U.S.A., e-mail: DrLowe@drlowe.com

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ABSTRACT. ***Introduction.*** All symptoms and most objectively verified abnormalities of fibromyalgia are common among patients with hypothyroidism or partial peripheral thyroid hormone resistance. In treatment trials, thyroid hormone therapy has reduced or eliminated fibromyalgia symptoms, and a long-term follow-up study showed that improvement with thyroid hormone therapy lasted 1-to-5 years. In a previous study by the authors, solicited female fibromyalgia patients had significantly lower resting metabolic rates and basal body temperatures than matched healthy controls. In this study, the resting metabolic rates and body temperatures of fibromyalgia patients previously evaluated at a specialty metabolic clinic were compared with healthy controls to whom they were matched.

Methods. Fifteen female fibromyalgia patients and 15 healthy females served as study subjects. Patients were clinical cases selected to match controls by sex, age, weight, and activity level. Resting metabolic rate (RMR) was measured by indirect calorimetry (MedGem®), basal body temperature with digital thermometers, and body composition by bioelectrical impedance. The mean measured resting metabolic rate (mRMR) was compared to percentages of the mean predicted RMR (pRMR) by two methods: fat-free weight (Sterling-Passmore equation: SP) and sex, age, height, and weight (Harris-Benedict and Mifflin-St. Joer equations: HB and MSt.J). Measurements were taken during the follicular phase of subjects' menstrual cycles.

Results. Patients had a lower mean mRMR (939.70 ± 216.04 kcal/d vs 1293.40 ± 166.34 kcal/d, $p = 0.00001$) and lower mRMRs as percentages of pRMRs (SP: -26.91 ± 13.36% vs -6.826 ± 12.55%, $p < 0.0001$. HB: -32.45 ± 13.48% vs -9.13 ± 9.51%, $p = 0.0001$; MSt.J: -27.96 ± 14.53% vs -5.089 ± 11.30%, $p = 0.0002$). Age and fat-free weight accounted for 62% of variability in controls'mRMRs. Fat-free weight, water as a percentage of body weight, and fibromyalgia symptom intensity accounted for 83% of the variability of patients' mRMRs. Patients' mean basal body temperature was significantly lower than that of controls (96.38 ± 0.98° F vs 97.54 ± 0.59° F, $p = 0.001$). Patients' serum free T_3 level was significantly lower than that of controls (3.18 ± 0.559 vs 3.75 ± 0.717 pg/mL, $p = 0.023$).

Conclusions. The patient group had a lower mean mRMR and lower mRMR as percentages of pRMRs. Patients also had a significantly lower mean basal body temperature. Neither calorie restriction nor low fat-free weight accounted for patients' lower RMRs. As in the previous study, fibromyalgia patients' normal fat-free weight argues against low physical activity with poor physical fitness as the mechanism of their low RMRs. Free T_4, free T_3, and TSH levels did not correlate with fibromyalgia measures or RMRs in either patient or control group. The lack of correlation does not rule out inadequate thyroid hormone regulation as the mechanism of the low RMRs because studies have not shown that these laboratory values reliably predict RMR values.

KEY WORDS. Resting metabolic rate, fibromyalgia, basal body temperature, body composition, TSH, free T_4, free T_3.

INTRODUCTION

"Fibromyalgia syndrome" is the diagnosis that clinicians most often give patients who have chronic widespread pain and abnormal tenderness. Most fibromyalgia researchers state that the etiology of the disorder is unknown. In doing so, they fail to account for a line of evidence that indicates that the main mechanism of fibromyalgia is inadequate thyroid hormone regulation. For some fibromyalgia patients, the inadequate regulation is due to hypothyroidism; for others, it is due to partial peripheral cellular resistance to thyroid hormone.

Evidence

The evidence that inadequate thyroid hormone regulation is the main mechanism of fibromyalgia falls into four categories: (1) symptoms, (2) studies of thyroid status, (3) objectively verified abnormalities, and (4) clinical trials with thyroid hormone therapy.

Symptoms. The symptoms of fibromyalgia are identical to symptoms of hypothyroidism and peripheral resistance to thyroid hormone.[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17]

Studies of Thyroid Status. A significant percentage of fibromyalgia patients have elevated thyroid autoantibodies[18][19] and an increased incidence of thyroid function test results consistent with primary and central hypothyroidism.[20][21][22][23][24][25][26] While the incidence of primary hypothyroidism in the general population is 1%-to-5%,[27][28] among fibromyalgia patients, the reported incidence is 10%-to-24%.[20][23][24][29][32] While the estimated incidence of central hypothyroidism in the general population is 0.00021%, among 92 fibromyalgia patients it was 43.5%.[21]

Objectively Verified Abnormalities. All other hypotheses of the etiology of fibromyalgia plausibly account for only a few objectively verified abnormalities among fibromyalgia patients. In contrast, at least 38 such abnormalities of fibromyalgia patients are credibly explained by inadequate thyroid hormone regulation of transcription, alternative splicing, or translation at the cellular level (see Table 1). All of these abnormalities have been reported to occur in either hypothyroidism, thyroid hormone resistance, or both.[1]

Clinical Trials with Thyroid Hormone Therapy. The only studies in which patients have recovered from their fibromyalgia status have been open[172][173][174][175][176] and blinded[177][178][179][180][181] clinical trials in which the patients were treated with thyroid hormone therapies other than T_4-replacement. A long-term follow-up study showed that compared to matched controls, fibromyalgia patients treated with thyroid hormone significantly improved; their improvement persisted through 1-to-5 years, depending on the time of follow-up since they began treatment.[182]

If inadequate thyroid hormone regulation is the mechanism of the symptoms and objective abnormalities of fibromyalgia, patients should have abnormally low resting metabolic rates (RMRs), as do patients with hypothyroidism[183][184] and/or peripheral thyroid hormone resistance.[57] In a previous study,[238] Lowe, Yellin, and Honeyman found that 15 female fibromyalgia patients had a significantly lower mean RMR than 15 matched healthy controls. Based on sex, age, height, and weight, the patients' mean RMR was 28.42% (± 15.82%) below normal. Based on the patients' fat-free weight, their mean RMR was 29.20% (± 17.43%) below normal. Patients' mean basal body temperature was significantly lower than that of controls (96.95 ± 0.63°F vs 97.54 ± 0.59°F, $p = 0.013$).

In the previous study,[238] patients were solicited from the general public for participation. In the present study, patients were selected from a large pool of cases at a clinic specializing in the diagnosis and treatment of hypometabolism. They were selected to match the healthy controls from the previous study.

The purpose of the present study was to compare the RMRs of our clinical fibromyalgia patients to those of matched healthy controls. Another purpose was to use regression analysis to test for the RMR-regulating factors that best account for the variability in study subjects' RMR values.

METHODS

The patients in the study were 15 females who met the American College of Rheumatology (ACR) criteria for fibromyalgia. Their fibromyalgia status was quantified by five measures: (1) the percentage of 36 body divisions in chronic pain, (2) presence of tender points (pressure-pain threshold determined by algometry), (3) scores on the Fibromyalgia Impact Questionnaire (a validated instrument for assessing functional ability[185]), (4) visual analog scales of 13 associated fibromyalgia symptoms, and (5) Zung's Self-Rating Depression Scale.

Researchers reviewed patients' records for three purposes: (1) to make sure that patients were not restricting calorie intake, (2) had not engaged in regular fitness training in the last six months (running, swimming, cycling, weight training, aerobics, or tennis), (3) but were regularly participating in work and routine life-maintenance activities (for example, shopping, house or yard work, local travel). No patient was included who had any disorder that could affect metabolic rate; the main disorders that excluded patients from the study were anemia, diabetes, and cardiovascular disease. Patients were also excluded if they used medications that could alter metabolism, such as β-adrenoceptor antagonists, metformin hydrochloride, thyroid hormone, oral contraceptives, or norepinephrine reuptake inhibitors.

The control group consisted of 15 females. Each failed to meet the ACR criteria for fibromyalgia and did not have an illness or injury that could influence resting metabolic rate. The subjects were classified as healthy based on a physical examination by a physician, blood tests, and psychological and health history questionnaires. Patients were matched to controls by sex, age, weight, absence of calorie restriction, and general physical activity level. Twelve applicants were excluded from the control group. They were excluded because they engaged in regular fitness training, were on a diet that could alter metabolism, or used a medication that could affect the metabolic rate.

Both premenopausal and postmenopausal subjects were included in the study. (Matching of patients to controls took menstrual status into consideration through the age criterion.) The purpose for this inclusion was to allow testing of the null hypothesis that menstrual status is unrelated to either measured RMR (mRMR) or predicted RMRs (pRMRs). No subjects smoked cigarettes or were pregnant. Laboratory biochemical tests performed included a comprehensive metabolic profile, lipid profile, AM cortisol, TSH, free T_3, and free T_4. Subjects were included regardless of their thyroid test results (whether consistent with euthyroidism, hyperthyroidism, or hypothyroidism). This was done so that statistical tests could be performed to determine whether these measures correlated with RMR values.

The Ethics Committee of the Fibromyalgia Research Foundation approved the study design. Each subject signed an informed consent after reading, and receiving an oral description of, the protocol. No subjects were paid for participating in the study; they all received copies of their test results.

Subjects were given oral and written instructions on how to prepare for laboratory biochemical testing and measurement of their RMR and body composition. They fasted overnight for ≥12 hours before blood draws at the medical laboratory (Boulder Community Reference Laboratory). After rising from sleep, they used house and automobile heating and extra clothing to remain comfortably warm. Having fasted for ≥12 hours, they drank no more than two 8 oz. glasses of water after awaking. They also carefully avoided physical and psychological stresses.

After the blood draw and upon arriving at the metabolic testing facility (the Center for Metabolic Health, LLC, in Boulder, Colorado) at 9 AM, each subject voided and disrobed to her underwear. A researcher then measured her weight on a balance beam scale (Healthometer, Continental Scale Corp., Bridgeview, IL) and measured her height with an attached stadiometer. Only the subject and tester were present. The temperature of the semidarkened, quiet room was such that it was comfortably warm for each subject. The subject relaxed supine on a comfortable table under a warm cover for ≥30 minutes. The tester visually monitored her to make sure she was lying still and was awake. Pulse and blood pressure were taken after RMR was measured.

Basal metabolic rates (BMRs) and RMRs are usually

Table 1. Same objectively verified abnormalities in fibromyalgia (FM) as compared to hypothyroidism (HO) or peripheral resistance to thyroid hormone (PRTH).

ABNORMALITIES	FM	HO or PRTH
Histological		
↑ Hyaluronic acid	34,35*	36*
↑ Ground substance proteoglycans	11,12,37-39	40-43
↓ Collagen	44,45	46,47
↓ Pyridinoline	48,49	50,51
↓ Procollagen III	52-54	36,55,56
↓ Hydroxyproline	44,45,48,49	47,50,57,58
↑ Mast cells	37,38,59	46,60-64
CSF		
↑ Substance P	65-68	69-72
↓ Dopamine (homovanillic acid)	73	74,75
↓ Tissue norepinephrine	73	76-78
↓ Urinary 5-hydroxyindole acetic acid	79	80
↓ Brain 5-hydroxytryptophan	73,81	82
↑ Nerve growth factor	83	84,85
Molecular		
↑ α-Adrenoceptors	86,87	88-95
Mitochondria		
Ragged red fibers	96,97	98,99
↓ Cytochrome-c-oxidase	100	98,99
Physiological		
Exercise intolerance	101-104	105-108
↓ Muscle relaxation time	109	110
Blunted cortisol response to ACTH	111,112	113
Orthostatic hypotension	114,115	116
Joint hypermobility	117,118	119
↓ Brain blood flow	120-122	123
↓ Peripheral blood flow	124-126	127
Blunted sympathetic and end-organ response to stress	101,115,128-131	132-135
Excess urination	136,137	138,139
↓ Delta-wave and nonrestorative sleep	140,141	138,142-144
High-energy phosphates		
↓ ATP	145	146-149
↑ Phosphodiesters	150-152	153
↑ Inorganic phosphate (Pi)	151	153,154
↓ Phosphocreatine (PCr)	145	146
↓ PCr/Pi ratio	145	154,155
Carbohydrate metabolism		
↑ Pyruvate	156-158	105,156,159
↓ LDH	150,156	150,156
↓ Intracellular pH	150	153,154
↓ Skeletal muscle glucose use	160	161-163
Endocrine		
↓ HPA axis function	131,164	165,166
↓ GH and IGF-1	167-169	170,171
↑ Hypothyroidism	20-26	n/a

*All numbers are references at the end of this paper.

Table 2. Anthropometric data (mean ± SD).

	Patients	Controls	p*
Age	47.73 ± 11.78 yrs	45.67 ± 11.83 yrs	0.635
Height	64.05 ± 2.85 in (162.68 ± 7.23 cm)	66.42 ± 2.80 in (168.70 ± 7.11 cm)	0.029
Weight	151.75 ± 39.78 lb (68.84 ± 18.04 kg)	155.36 ± 34.12 lb (70.47 ± 15.48 kg)	0.792
BMI	25.88 ± 5.90 kg/m^2	24.65 ± 4.51 kg/m^2	0.527
FFW	93.42 ± 16.26 lb (42.38 ± 7.38 kg)	101.94 ± 16.33 lb (46.24 ± 7.41 kg)	0.164
% Body fat	36.93 ± 6.59	33.42 ± 6.04	0.140
FW	57.85 ± 24.84 lb (26.24 ± 11.27 kg)	53.42 ± 20.21 lb (24.23 ± 9.17 kg)	0.596
BBT	96.38 ± 0.98° F (35.76 ± 0.54° C)	97.54 ± 0.59° F (36.41 ± 0.33° C)	0.001

*Difference significant (independent t-tests) at $p < .05$ level.

lowest during menstruation and are elevated during the luteal phase of the menstrual cycle.[186][187] For this reason, premenopausal patients underwent indirect calorimetry during the follicular phase of their menstrual cycle.

One or the other of two testers, using a hand-held indirect calorimeter (the MedGem®, Healthetech, Golden, Colorado), measured the RMRs of all subjects. The device measures VO_2 and calculates RMR using a modified Weir equation. In the equation, a constant respiratory quotient value of 0.85 ($RMR = 6.931 \times VO_2$)[188] is used. Researchers have reported that the MedGem® measured VO_2 and calculated RMR as accurately and reliably as reference calorimeters.[189][190][191][192]

One research group reported that the energy cost of subjects holding the MedGem® is 255 ± 84 kJ/day. When adjusted for this increase, however, mRMR by the MedGem® did not significantly differ from mRMR by the Sensormedics® 2900 indirect calorimeter.[189] To avoid the increase in RMR from holding the instrument, each subject's arm and hand were supported with cloth padding so that muscle contraction was not necessary. After measuring the RMR, the measurement was converted to percentages of RMR predicted by the subject's fat-free weight (Sterling-Passmore equation) and sex, age, height, and weight (Harris-Benedict and Mifflin-St. Joer equations).

In preparing for their body composition to be measured, subjects avoided alcohol for 24 hours and drank up to two glasses of water on the morning of the test. After the tester measured a subject's RMR, he or she then measured the subject's body composition by 4-electrode bioelectrical impedance (Biodynamics® Model 310, Seattle, WA).

Statistical Analysis

Data are expressed as means ± standard deviations (SD). We used t-tests to determine differences between anthropometric variables and between mean mRMR, pRMRs, and percentages of pRMRs. Correlations between continuous and dichotomous variables were determined by means of the point-biserial correlation coefficient. Stepwise multiple regression analysis (R^2) was used to determine which factors known to regulate RMR significantly accounted for the variability of mRMR and percentages of pRMRs. The level of significance was set at $p \le 0.05$. SPSS for Windows (SPSS, Inc., Chicago, IL), VassarStats: Website for Statistical Computation, and Microsoft® Excel 2002 were used for statistical analyses.

RESULTS

Anthropometrics and RMR

With the exception of height and basal body temperature, patients and controls did not significantly differ on anthropometric measures (see Table 2). Patients' mean basal body temperature was significantly lower than that of controls (96.38 ± 0.98° F vs 97.54 ±0.59° F, $p = 0.001$). As Table 3 shows, the groups' mRMRs also significantly differed (939.70 ± 216.04 kcal/d vs 1293.40 ± 166.34 kcal/d, $p = 0.00001$), but their pRMRs by fat-free weight (SP equation) and by sex, age, height, and weight (HB and MStJ equations) did not differ.

RMR and Regression

We used regression analysis to determine which if any factors known to regulate RMR best accounted for the variability in RMR and basal body temperature values. Table 4 summarizes results of the R^2 analyses for both groups. It shows how closely the variability of independent measures mirrored the variability of mRMR and mRMR as percentages of pRMRs.

Controls. The variance of fat-free weight most closely resembled the variance of mRMR and accounted for 34% of the variability in mRMR. (The Pearson correlation coefficient showed that fat-free weight positively correlated with mRMR: $r = 0.5850$, $p = 0.022$.) Age and fat-free weight together accounted for 62% of the variability in mRMR. (Pearson showed that age negatively correlated with mRMR: *r* = -0.5209, *p* = 0.046.)

Also for controls, the variance of weight best fit the variance of mRMR as a percentage of pRMR by fat-free weight (Sterling-Passmore equation). Weight, then, accounted for 49% of that variability. (By the Pearson correlation coefficient, the correlation of the two variables was significantly negative: *r* = -0.6999, *p* = 0.004.)

The variance of controls' fat weight most closely resembled that of mRMR as a percentage of pRMR by sex, age, height, and weight (Mifflin-St. Joer equation), accounting for 33% of the variability. BMI and fat weight accounted for 64% of the variance, and BMI, fat weight, and pain distribution accounted for 75%.

And finally, the variability of fibromyalgia symptom intensity (FibroQuest score) most closely fit that of mRMR as a percentage of pRMR by sex, age, height, and weight (Harris-Benedict equation), and accounted for 32% of the variance. This mRMR value also positively correlated with symptom intensity (*r* = 0.5640, *p* = 0.029).

Patients. As for controls, the variance of patients' fat-free weight best fit the variance of mRMR, accounting for 53% of the variability. Together, the variance of patients' fat-free weight and water as a percentage of body weight accounted for 69%. And when we combined the variance of fat-free weight, water as a percentage of body weight, and fibromyalgia symptom intensity, these three independent variables accounted for 83% of the variations in mRMR.

The Pearson correlation coefficient showed that patients' fat-free weight positively correlated with mRMR (*r* = 0.7210, *p* = 0.002). However, the test showed no significant correlation between mRMR and either water as a percentage of body weight (-0.2060, *p* = 0.461) or fibromyalgia symptom intensity (-0.4183, *p* = 0.121).

No independent measure's variability fit that of mRMR as a percentage of pRMR by fat-free weight (SP) or by sex, age, height, and weight (either HB or MStJ). Also, we found no significant correlations between these RMR values and any independent variable tested.

Basal Body Temperature

In stepwise regression analysis, no independent measure accounted for the variability of controls' basal body temperature. For patients, water as a percentage of fat-free weight was the only independent measure that accounted for the variability of basal body temperature. This measure strongly negatively correlated with the temperature (*r* = -0.6178, *p* = 0.0141) and accounted for 38% of the variability of the temperature.

Thyroid Function Tests

TSH and free T_4 levels did not significantly differ between groups. However, patients had a significantly lower mean free T_3 level than did controls (3.18 ± 0.559 pg/mL vs 3.75 ± 0.717 pg/mL, *p* = 0.023). In neither group did TSH, free T_4, or free T_3 levels significantly correlate with mRMR or mRMRs as percentages of pRMRs. Also, in neither group did the laboratory test levels significantly correlate with any fibromyalgia measure.

Menopausal Status

Postmenopausal controls had a significantly lower mean mRMR (1221.75 kcal/d vs 1375.29 kcal/d, *p* = 0.0365) and percentage of pRMR by the Harris-Benedict equation using sex, age, height, and weight (-12.95% vs -4.77%, *p* = 0.0484). The percentage of pRMR by the Sterling-Passmore equation using fat-free weight was almost significantly lower for postmenopausal controls (-11.33% vs -1.67%, *p* = 0.0714). The basal body temperature of postmenopausal controls was significantly higher than that of premenopausal controls (97.81° F vs 97.23° F, *p* = 0.0558), as were their T_4 levels (1.389 ng/dL vs 1.036 ng/dL, *p* = 0.039). The basal pulse rate of postmenopausal controls was almost significantly higher (72.08 bpm vs 67.12 bpm, *p* = 0.0574). And, the mean fibromyalgia symptom intensity of postmenopausal controls was sig-

Table 3. Measured RMR and predicted RMRs (mean ± SD).

	Patients	Controls	*p**
mRMR	939.70 ± 216.04 kcal/d (3931.71 ± 903.93 kJ/d)	1293.40 ± 166.34 kcal/d (5411.59 ± 695.95 kJ/d)	0.00001
pRMR by SP**	1289.20 ± 224.42 kcal/d (5394.00 ± 938.98 kJ/d)	1406.77 ± 225.38 kcal/d (5885.93 ± 942.97 kJ/d)	0.16329
pRMR by HB***	1391.41 ± 166.54 kcal/d (5821.66 ± 696.81 kJ/d)	1427.54 ± 152.47 kcal/d (5972.81 ± 637.92 kJ/d)	0.54049
pRMR by MStJ****	1308.88 ± 190.71 kcal/d (5476.36 ± 797.91 kJ/d)	1372.71 ± 181.00 kcal/d (5743.40 ± 757.30 kJ/d)	0.35518

*Difference significant (independent t-tests) at *p* < .05 level.
**SP: Sterling-Passmore equation, uses FFW.
***HB: Harris-Benedict equation, uses sex, age, height, weight.
****MStJ: Mifflin-St. Joer equation, uses sex, age, height, weight.

nificantly lower than that of premenopausal controls (2.29 vs 3.47, p = 0.023).

Compared to premenopausal patients, postmenopausal patients had a lower mean basal body temperature (95.92° F vs 97.07° F, p = 0.0092) and basal pulse rate (61.10 bpm vs 69.47 bpm, p = 0.0385). Postmenopausal patients also had a significantly higher free T_3 level (3.46 pg/mL vs 2.76 pg/mL, p = 0.0111). TSH and free T_4 levels did not significantly differ between post- and premenopausal patients, and no RMR values significantly differed between the two patient groups.

Depression Status

When grouped as nondepressed or depressed, controls did not differ in RMR values, fibromyalgia scores, or thyroid function test results. However, when patients were grouped according to depression level, those with moderate-to-severe depression had a significantly wider pain distribution (34.63% vs 21.21%, p = 0.0254) than did patients with no depression-to-mild depression.

DISCUSSION

Female fibromyalgia patients in this study had significantly lower RMR values and basal body temperatures than did matched healthy controls. These results are consistent with those from our previous study[238] of the RMRs and basal body temperatures of fibromyalgia patients.

RMR Values

Patients and controls did not significantly differ in pRMRs calculated by fat-free weight or by sex, age, height, and weight (see Table 3). However, patients' mRMR was significantly lower than that of controls (939.70 ± 216.04 kcal/d vs 1293.40 ± 166.34 kcal/d, p = 0.00001). Patients' mean mRMR was 26.91% below their pRMR calculated from fat-free weight (see Graph 1 for a data point-line display of the differences; also see Table 5). Using sex, age, height, and weight, their mRMR was 32.45% below their pRMR (Harris-Benedict equation; Graph 2 and Table 5), and 27.96% below pRMR (Mifflin-St. Joer equation; Table 5). Compared to the control group, then, the patient group was severely hypometabolic.

Controls. For controls, mRMR significantly positively correlated with fat-free weight and significantly negatively correlated with age. These results are consistent with other reports for healthy controls.[186][193][194][195]196][197][198][199] Weight significantly negatively correlated with mRMR as a percentage of pRMR by fat-free weight (r = -0.6999, p = 0.004); that is, heavier controls had lower mRMRs. Despite this, mRMR did not significantly differ from mRMR as a percentage of pRMR by fat-free weight.

Also for controls, fat weight, BMI, and pain distribution accounted for 75% of the variance of mRMR expressed as a percentage of pRMR by sex, age, height, and weight (Mifflin-St. Joer equation; see Table 4). BMI did not significantly correlate with this RMR value, though fat weight did inversely (r = -0.5714, p = 0.026). In other words, the higher the fat weight, the lower the mRMR. This is not consistent with what researchers generally report. For example, Ravussin et al. found that the mean RMR increases stepwise from nonobese controls, to moderately obese subjects, on to severely obese subjects.[195,p.566] They stated that the higher RMRs in heavier subjects resulted from their higher oxygen consumption in daylight hours, and that 8% of the higher RMR of obese subjects resulted from factors such as the increased energy cost of moving their heavier weight about. Goran reported that the effect of fatness on energy expenditure is negligible other than a small effect on RMR. He noted that patients with more fat are less likely to be physically active, but when they are active, the energy cost of moving about is higher than people with less fat.[33,p.355] From these reports, one would expect the opposite from our test results: that our controls with higher fat weight would have had higher RMR values rather than lower.

Of particular interest is the finding that the lower the controls' mRMRs as a percentage of pRMR (Mifflin-St. Joer equation) were, the higher was the percentage of their bodies in pain. Widespread pain is common among patients who are hypometabolic from hypothyroidism, peripheral thyroid hormone resistance, or a sedentary lifestyle.[1] It is possible that our controls were mildly hypometabolic due to their sedentary lifestyle (a matching criterion for inclusion in the study), and because of this, had some degree of chronic pain. Nonetheless, the controls' pain distribution was significantly lower than that of patients (3.73 ± 3.97% vs 26.07 ± 12.66%, p = 0.00003).

The controls' sedentary lifestyle may also account for the positive correlation (r = 0.5640, p = 0.029) between fibromyalgia symptom intensity and mRMR as a percentage of pRMR using sex, age, height, and weight (Harris-Benedict equation). Controls' symptom intensity, however, was significantly lower than that of patients (2.84 ± 1.048 vs 6.65 ± 1.335, p = 0.00000001).

Patients. The variance of fat-free weight best fit the variance of mRMR, accounting for 53% of the variability (Table 4). Of all the independent variables measured in patients, only fat-free weight significantly correlated with mRMR and the relationship was strong (r = 0.7210, p = 0.002). Despite these two findings, the overall evidence does not indicate that patients' mRMR was a function of their fat-free weight.

One might presume that the close fit of the variability of fat-free weight, and the strong positive correlation, with mRMR indicate that patients' low mRMRs were due to low fat-free weight. From that, one might also presume that the low fat-free weight was due to lost skeletal muscle mass from low physical activity. However, as is clear from Graph 1, these presumptions are not correct. The top trend line in the graph represents the pRMR calculated directly from patients' fat-free weight using the Sterling-Passmore equation. The bottom trend line represents the patients' mRMRs. The Sterling-Passmore equation—using patients' actual fat-free weight—predicted that patients' mRMR would be 26.91% higher than it actually was.

In addition, as Table 2 shows, the fat-free weight of controls and patients did not significantly differ. As Table 3 shows, however, the patients' mean mRMR was significantly lower than that of controls (939.70 ± 216.04 kcal/d vs 1293.40 ± 166.34 kcal/d, p=0.00001).

Moreover, patients' mean creatinine level was within the reference range (value: 0.83; range: 0.5-1.2 mg/dL). Controls' creatinine level was slightly higher (87 mg/dL), but the groups' levels did not significantly differ. In that creatinine is considered to reflect muscle mass,[201] patients' mean creatinine level, like their fat-free weight, indicates that they did not have low muscle mass. As in our first study of the RMRs of fibromyalgia patients,[238] fat-free weight and creatinine values argue against low physical activity as a mechanism of patients' low RMRs. The values also contradict the hypothesis that physical deconditioning is the etiology of fibromyalgia patients' symptoms.[202]

On the other hand, the sedentary lifestyles of the two groups may be associated to a small degree with widespread pain and fibromyalgia symptoms in both groups. We hasten to add, though, that since many fibromyalgia patients only become sedentary after their symptoms become severe, their sedentary lifestyle is most likely a result, rather than a cause, of their fibromyalgia.

Table 4. Independent variables* as predictors of measured RMR, and measured RMR expressed as percentages of predicted RMRs.

Controls	**Number of variables**	R^2
mRMR	Fat-free weight	0.3423
	Age, fat-free weight	0.6202
mRMR as percentage of pRMR (SP**)	Weight	0.4898
mRMR as percentage of pRMR (HB***)	Fibromyalgia symptom intensity^	0.3181
mRMR as percentage of pRMR (MStJ****)	Fat weight	0.3265
	BMI, fat weight	0.6351
	BMI, fat weight, pain distribution	0.7503
Patients	**Number of variables**	R^2
mRMR	Fat-free weight	0.5278
	Fat-free weight, water as % body weight	0.6902
	Fat-free weight, water as % body weight, fibromyalgia symptom intensity^	0.8286
mRMR as percentage of pRMR (SP**)	None	
mRMR as percentage of pRMR (HB***)	None	
mRMR as percentage of pRMR (MStJ****)	None	

*Independent variables: age, height, weight, FFW, FW, BMI, % body fat, total body water, water as % of body weight, water as % of fat-free weight, TSH, FT_3, FT_4, basal body temperature, basal pulse rate, ^FibroQuest score, Fibromyalgia Impact Questionnaire score, mean tender point in kg/cm^2, and pain distribution.
**SP: Sterling-Passmore equation, uses FFW.
***HB: Harris-Benedict equation, uses sex, age, height, weight.
****MStJ: Mifflin-St. Joer equation, uses sex, age, height, weight.

In that patients' fat-free mass was not abnormally low, it may seem a paradox that regression analysis showed a tight fit between the variability of fat-free weight and patients' mean mRMR. The apparent paradox may come from a term that some researchers, ourselves among them,[238] have used to describe the close-fitting variances of independent and dependent variables. When the variance of a particular independent variable "fits" the variance of the dependent variable more closely than the variances of other independent variables, researchers often write that the particular independent variable "best predicted" the dependent variable. This is appropriate when, among healthy controls, we state that fat-free weight best predicts mRMR. In general, fat-free weight is the strongest determinant of mRMR,[186][193][194][195][196][197][198][199] and accounts for some 82% of the variance in mRMR.[200] To some, however, this terminology always implies a causative relationship between the two variables—the independent variable causing the dependent variable.

However, even when two variables with tightly-fitting variances are causatively related in general, their variances may tightly fit only coincidentally. We emphasize, then, that for patients in our study, the significant fit of the variances of fat-free weight and mRMR, and their strong positive correlation, do not show that patients' low mRMRs were caused by low fat-free weight. We can consider the significant fit, in this case, to be coincidental because enough other evidence contradicts a causative relationship.

Of nineteen tested independent variables that might influence patients' RMR values, none significantly fit the variances of mRMR as percentages of pRMRs (using the Sterling-Passmore, Harris-Benedict, and Mifflin-St. Joer equations, see Table 4). Furthermore, as we have indicated elsewhere,[238] the thyroid laboratory values we tested (TSH, free T_3, and free T_4) are dubious as predictors of RMR. Hence, the lack of significant correlation and the lack of significant fit between these values and RMR values do not rule out inadequate thyroid hormone regulation as the underlying mechanism of patients' low RMRs.

Basal Body Temperature

The significantly lower mean basal body temperature of patients compared to controls (96.38 ± 0.98° F vs 97.54 ± 0.59° F, p = 0.001) is consistent with hypothyroidism.[225][226] From the beginning of thyroid hormone therapy, temperature has been important to many clinicians in the diagnosis and treatment of hypothyroid patients.[1,p.842] For example, in 1891, physician George Murray reported the first hypothyroid patient treated with thyroid extract in the United Kingdom.[242] Before treatment, her temperature varied between 95.6° F and 97.2° F. After Murray began injecting her with sheep thyroid extract, her temperature rose to 98.2° F.[243] Murray titrated each of his patient's thyroid extract dosage according to changes in pulse rate and temperature.

Today, many alternative/complementary physicians consider a low basal body temperature an objective indication of hypothyroidism when the patient has symptoms characteristic of the disorder.[31][218][244][245][246][247][248][249] Barnes defined the reference range for basal body temperature as 97.8° F-to-98.2° F.[244,p.46] Using this range, both our patients' and controls' mean temperatures were abnormally low (96.38 ± 0.98° F and 97.54 ± 0.59° F). Nonetheless, the patients' mean temperature was significantly lower than that of controls. The patients' low temperatures and low RMR values indicate that their oxidative metabolism and heat-generating enzyme systems were inadequately regulated by thyroid hormone.

Differences Between Premenopausal and Postmenopausal Groups

We found several differences between premenopausal and postmenopausal groups among both controls and patients.

Controls. Seven controls were premenopausal; eight were postmenopausal. An unexpected finding is that the mean fibromyalgia symptom intensity of premenopausal controls was significantly higher than that of postmenopausal controls (3.47 vs 2.29, p = 0.023). However, the mean symptom intensity (scale ranges from 0-10) of all controls combined was significantly lower than that of patients (2.84 vs 6.65, p < 0.000000001).

The premenopausal controls had a significantly lower mean basal body temperature (97.138° F vs 97.810° F, p = 0.0361). This raises the possibility of suboptimal RMRs, although no RMR values were significantly different between the two groups of controls.

As we stated above, fibromyalgia symptoms such as widespread pain are common among those who are hypometabolic from hypothyroidism, peripheral thyroid hormone resistance, or a sedentary lifestyle. In view of this, it is possible that our control subjects were mildly hypometabolic due to their sedentary lifestyle. Because of this, they may have had mild symptoms of hypo-

Table 5. Measured RMR as percentages of predicted RMRs (mean ± SD).

Equation	Patients	Controls	p*
% of pRMR (SP**)	-26.91 ± 13.36	-6.83 ± 12.55	0.0001
% of pRMR (HB***)	-32.45 ± 13.48	-9.13 ± 9.51	0.0001
% of pRMR (MStJ****)	-27.96 ± 14.53	-5.09 ± 11.30	0.0002

*Difference significant (independent t-tests) at p < .05 level.
**SP: Sterling-Passmore equation, uses FFW.
***HB: Harris-Benedict equation, uses sex, age, height, weight.
****MStJ: Mifflin-St. Joer equation, uses sex, age, height, weight.

metabolism that for purposes of classification we consider symptoms of fibromyalgia.

It is within the realm of possibility, though, that the premenopausal controls had suboptimal metabolism due to lower free T_4 levels. The premenopausal controls' mean level of 1.036 ng/dL was slightly above the cutoff point (0.99 ng/dL) between the first and second quartiles of the reference range of 0.59 ng/dL-to-2.19 ng/dL. By contrast, the T_4 level of postmenopausal controls, 1.389 ng/dL, was at the midpoint of the upper end of the reference range. Point biserial correlation coefficient showed that premenopausal controls' levels were significantly lower than those of postmenopausal controls (1.036 ng/dL vs 1.389 ng/dL, $p = 0.039$). Such hair-splitting distinctions with thyroid function tests, however, are dubious in view of the rapid significant changes in levels throughout the day.[241]

Patients. Six patients were premenopausal; nine were postmenopausal. Postmenopausal patients had significantly lower basal pulse rates than premenopausal patients (61.1 bpm vs 69.47 bpm, $p = 0.039$). They also had significantly lower basal body temperatures (95.919° F vs 97.072° F, $p = 0.0093$). However, postmenopausal patients had significantly higher free T_3 levels than did premenopausal patients (3.46 pg/mL vs 2.76 pg/mL, $p = 0.0112$). As we have previously suggested,[238,p.CR286] a higher serum free T_3 level in patients with lower temperatures and pulse rates may indicate lower intracellular T_3 levels. Lower intracellular levels may result in lower metabolism with consequent lower heart rates and temperatures.

TSH and free T_4 levels did not significantly differ between pre- and postmenopausal patients. No RMR values significantly differed between the two patient groups.

Differences Related to Severity of Depression

Controls. When grouped as depressed or nondepressed, controls did not differ in RMR values, thyroid function test results, or fibromyalgia scores.

Patients. According to Zung's Self-Rating Depression Scale, all patients had some degree of depression. Seven patients had mild depression; eight had moderate-to-severe depression. There were no differences between the two depression groups' temperatures, pulse rates, thyroid laboratory test results, Fibromyalgia Impact Questionnaire scores, or fibromyalgia symptom intensity (other than severity of depression).

However, patients with moderate-to-severe depression had a lower mean tender point pressure/pain threshold than mildly depressed patients (1.7513 kg/cm^2 vs 2.5457 kg/cm^2, $p = 0.0179$). The moderate-to-severe depression group also had a significantly wider pain distribution (32.05% vs 19.25%, $p = 0.046$).

There are at least three possible explanations for the association of worse depression with greater tenderness and wider pain distribution: (1) patients with more widely distributed pain may have been more depressed because of more suffering; (2) the slumped posture often chronically assumed by depressed patients may have induced pain at multiple biomechanical stress vectors associated with the slumping, as has been reported in fibromyalgia patients;[237] and (3) as the authors believe to be most likely, both a wider pain distribution and depression may have been concomitant effects of inadequate thyroid hormone regulation.[1]

Increased pain perception is predictable from inadequate thyroid hormone regulation. As we explained in detail in the report of our previous RMR study,[328,p.CR286] thyroid hormone normally inhibits excess synthesis and secretion of substance P, a compound that augments pain perception.[69][70][72][222][223] It does so by regulating transcription of the gene that codes for preprotachykinin-A, the precursor of substance P and its receptor.[222][224] When rats were made hypothyroid, the substance P concentration in their dorsal horn nociceptive neurons increased as much as 100%.[71][72] Administering thyroid hormone lowered the concentration to normal.[70][71] Researchers have reported that the substance P level in fibromyalgia patients' cerebrospinal fluid is 90%-to-300% higher than normal.[65][68] As we formerly conjectured, the reduction of fibromyalgia patients' pain and tenderness in T_3 phases of our three double-blind trials, and the return of pain and tenderness in placebo phases, may have resulted respectively from decreases and increases of the patients' substance P levels.[177][178][179]

Of course, in addition to depression and pain, inadequate thyroid hormone regulation also credibly accounts for the two most important findings in this study: patients' lower metabolic rates and lower body temperatures.

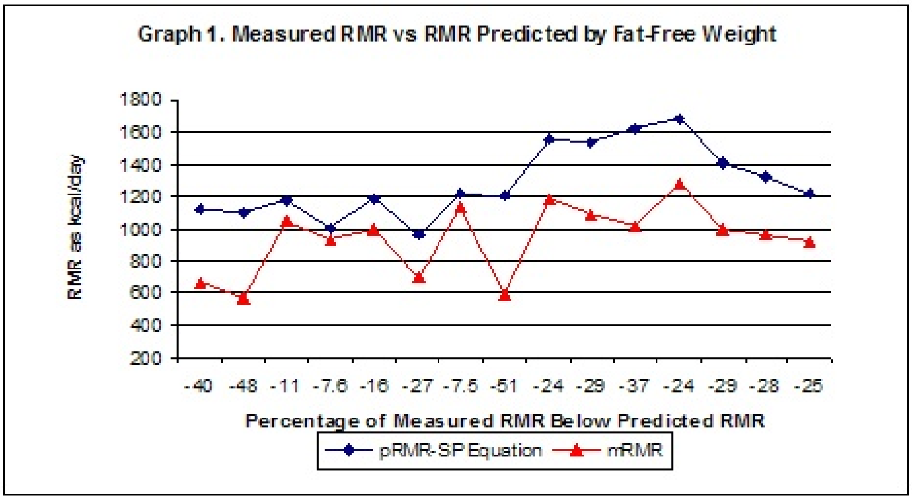
Thyroid Function Tests

In our previous study,[238] patients' TSH level positively correlated with their pain distribution. This raised the possibility that pain distribution in fibromyalgia is associated with primary hypothyroidism. This putative association is consistent with previous studies showing a high incidence of primary hypothyroidism among fibromyalgia patients.[20][21][24][29][219] In the present study, however, neither TSH, free T_3, nor free T_4 levels correlated with any measure of fibromyalgia.

In the previous study,[238] the mean free T_3 level of 4 pg/mL was within the reference range (2.77 pg/mL-to-5.27 pg/mL), and the mean free T_3 levels of patients and controls did not significantly differ. However, the mean free T_3 level inversely correlated with pressure-pain threshold ($r = -0.5499$, $p = 0.0337$).

In this study, patients' mean free T_3 level, 3 pg/mL, was in the lower quartile of the reference range (2.77 pg/mL-to-5.27 pg/mL) and was significantly lower than that of controls. Controls' free T_3 level of 4 pg/mL was in the middle of the range (midpoint: 4.02 pg/mL). The differences in free T_3 levels of patients and controls in the two studies are probably of no importance in that the levels of free T_3, just as those of TSH and free T_4, significantly vary every 15 minutes.[241]

As we documented in our previous report of low RMRs among women with fibromyalgia,[238] studies have not shown that thyroid function test results reliably correlate with RMR values.[214][215][216][217] Because of this, the lack of correlation between the results of thyroid function tests (TSH, free T_3, and free T_4) and RMR values in this study does not rule out inadequate thyroid hormone regulation as the mechanism of our patients' low RMR values.



Limitations

The limitations of this study are the same as in the first.[238] We are aware of at least three.

Hormone Deficiencies. A deficiency of growth hormone, insulin-like growth factor-1,[203][204] or testosterone[205][206] can lower RMR values by lowering fat-free weight. We did not measure levels of these hormones so we cannot exclude the possibility of one or more deficiencies. But the fat-free weight and creatinine levels of our patients suggest that such deficiencies are unlikely causes of their low RMR values.

Calorie Intake and Expenditure. In our previous study, patients and controls objected to keeping diet and physical activity logs. For this reason, in the present study, we did not require subjects to keep the logs.

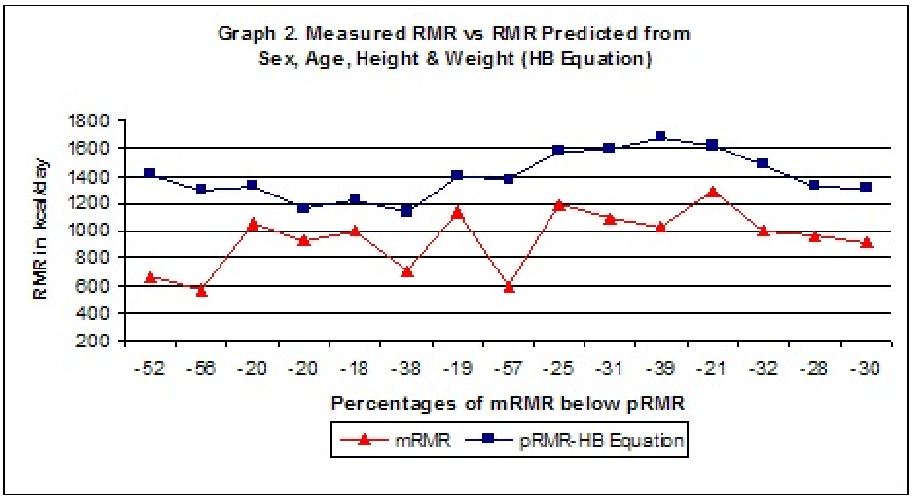
In trying to keep diet logs early in our first study,[238] several subjects substantially underreported their calorie intake. The logs showed that calorie intake was 32% below calorie expenditure due to underreporting. Such underreporting is common in studies in which subjects keep logs;[229][230][231][232][233][234][235][236] underreporting has ranged from 20%-to-30%[230][235] and 40%.[231][232][233]

Because subjects did not keep diet and activity logs in the present study, we examined the daily food consumption that patients reported on their medical history and health status form (FibroQuest Long Form). We ensured that they were not restricting calorie intake and that they were neither completely sedentary nor engaged in regular fitness training. The same information was acquired from healthy controls through careful questioning.

Examining reports from the patients' FibroQuest Long Forms and questioning controls did not allow an actual measurement of subjects' calorie intake or energy expenditure. This shortcoming should be corrected in future studies by the use of both a computer-based diet assessment program and a computerized device, such as an accelerometer, to calculate energy expenditure through measured activity level.

Source of Possible Inadequate Thyroid Hormone Regulation. The TSH, free T_4, and free T_3 tests assess only the function of the pituitary-thyroid axis. When the test results are within their reference ranges, they do not rule out two types of inadequate thyroid hormone regulation that can lower RMR: central hypothyroidism and partial peripheral resistance to thyroid hormone.[57][227] In previous studies, our research group found that 44% of fibromyalgia patients had test results consistent with central hypothyroidism.[20][21] Because the dynamic TRH-stimulation test that can identify patients with central hypothyroidism is no longer available in the United States, the patients in this study were not tested for possible central hypothyroidism.

Evidence indicates that approximately 35% of fibromyalgia patients have peripheral thyroid hormone resistance.[228] Four clinical criteria are necessary to determine that a patient has peripheral resistance: the patient (1) is euthyroid (according to thyroid function test results including the TRH stimulation test, if possible) before beginning the use of T_3; (2) recovers from hypothyroid-like fibromyalgia symptoms and signs with supraphysiologic dosages of T_3; (3) has an extremely high serum free T_3 level once reaching his or her effective dose of T_3; and (4) has no evidence of tissue thyrotoxicosis, according to the results of serial ECGs, serum and urine biochemical tests, and bone densitometry.[1][30] Because patients in this study


Graph 2. Measured RMR vs RMR Predicted from Sex, Age, Height & Weight (HB Equation)

did not undergo treatment, we do not know if any of them would have met these criteria.

CONCLUSIONS

Our data indicate that among controls, lower RMRs were associated with a small degree of two fibromyalgia features: symptom intensity and pain distribution. These features were mild and were significantly lower than among fibromyalgia patients. A possible mechanism of these features is the controls' sedentary lifestyle, which was a criterion for inclusion in this study. If so, this lends credibility to an ancient observation by writers such as Maimonides, Galen, and Sidenham:[1,p.59] a sedentary lifestyle causes some people to develop chronic aches and pains with fatigue. These are symptoms that today we might diagnosis as fibromyalgia. However, low physical fitness is highly unlikely to account for our fibromyalgia patients' more severe symptoms and extreme hypometabolism. This is unlikely because controls and patients were matched according to physical activity level.

As in our first study of the RMRs and basal body temperatures of fibromyalgia patients,[238] patients in this study had a significantly lower mean RMR and basal body temperature than did matched healthy controls. The lower RMRs did not appear to be a result of calorie restriction, lower physical activity level, loss of fat-free weight, menstrual phase, or metabolism-lowering drugs such as β-blockers.

Patients mean free T_3 level was within the reference range but was significantly lower than that of controls. TSH and free T_4 levels did not differ between the groups. In neither group did TSH, free T_3, or free T_4 levels correlate with any RMR value or any measure of fibromyalgia status. For two reasons, however, inadequate thyroid hormone regulation cannot be ruled out as the mechanism of patients' lower RMRs: (1) TSH, free T_3, and free T_4 levels have not been shown to reliably correlate with RMR values, and (2) these laboratory tests evaluate only pituitary-thyroid axis function and cannot identify central hypothyroidism or partial peripheral resistance to thyroid hormone.

In summary, none of the variables we tested appeared to have a causative relationship to our patients' low RMR values and low basal body temperatures. The low measures, however, are characteristic of inadequate thyroid hormone regulation. In view of this and our inability to eliminate inadequate thyroid hormone regulation as a causative factor, it remains the most likely mechanism of our patients' low metabolism and low basal temperatures.

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Comparison of Cynomel and Hypo Support Formula: Their Physiological Effects

(Full Text Free in pdf format)

Dr. John C. Lowe*

*Director of Research: Fibromyalgia Research Foundation

Contact: Dr. John C. Lowe
drlowe@FibromyalgiaResearch.org, drlowe@drlowe.com
www.FibromyalgiaResearch.org, www.drlowe.com

Apology

This abstract introduces a study report about a dietary desiccated thyroid product called "HSF." I have written a short editorial apology about two points in the report: (1) a possible error in the report concerning HSF being "organic," and (2) a claim about HSF that in my opinion is false, that is, that it is "thyroxine-free." Some retailers are currently using the report to promote sales of HSF. Because of that, we have corrected the possible error in this reports. Editorial apology.

ABSTRACT. This study compared the clinical effectiveness of a dietary desiccated thyroid product (Hypo Support Formula or HSF), to that of a synthetic T3 product (Cynomel). **Methods:** A single-subject two-phase repeated-measures study design was used. Comparisons were made between two study phases: the Cynomel phase followed by the HSF phase. Clinical evaluations included four basal measures: metabolic rate (BMR), heart rate (BHR), axillary temperature (BAT), and blood pressure (BBP). Other measures were body composition, mean hypothyroid symptoms intensity, Zung's depression scale, and pain distribution. Study subjects were a female stable on 87.5 mcg of Cynomel for two years, and a male stable on 150 mcg of Cytomel or Cynomel for 24 years. In the Cynomel phase, the female remained on Cynomel through 10 evaluations on different days; the male subject remained on Cynomel through 12 evaluations. After the transition from Cynomel to HSF, she then had 10 more evaluations; the male subject had 12 more evaluations. **Results:** The female's temperature was the same in both phases. In the HSF phase, her heart rate was significantly lower and her basal metabolic rate significantly higher. A noteworthy improvement for her in the HSF phase was virtual elimination of lifelong, severe hyperhidrosis. This has persisted now for 3.5 months. The male subject's BMR and BAT were not different in the two phases. However, during the HSF phase, he had a significantly lower heart rate, diastolic blood pressure, pain distribution, pain intensity, and mean intensity of hypothyroid symptoms. **Conclusions:** Both HSF and Cynomel were effective, but HSF provided additional improvements.

Keywords. Basal metabolic rate • Basal temperature • Cynomel • Cytomel • Desiccated thyroid • Hypo Support Formula • RLC Labs • Triiodothyronine

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Comparison of Cynomel and Hypo Support Formula: Their Physiological Effects

John C. Lowe[†]

[†]Director of Research: Fibromyalgia Research Foundation
Contact: Dr. John C. Lowe, drlowe@FibromyalgiaResearch.org drlowe@drlowe.com

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Abstract. This study compared the clinical effectiveness of a dietary organic natural desiccated thyroid product (Hypo Support Formula or HSF), to that of a synthetic T_3 product (Cynomel). **Methods:** A single-subject two-phase repeated-measures study design was used. Comparisons were made between two study phases: the Cynomel phase followed by the HSF phase. Clinical evaluations included four basal measures: metabolic rate (BMR), heart rate (BHR), axillary temperature (BAT), and blood pressure (BBP). Other measures were body composition, mean hypothyroid symptoms intensity, Zung's depression scale, and pain distribution. Study subjects were a female stable on 87.5 mcg of Cynomel for two years, and a male stable on 150 mcg of Cytomel or Cynomel for 24 years. In the Cynomel phase, the female remained on Cynomel through 10 evaluations on different days; the male subject remained on Cynomel through 12 evaluations. After the transition from Cynomel to HSF, she then had 10 more evaluations; the male subject had 12 more evaluations. **Results:** The female's temperature was the same in both phases. In the HSF phase, her heart rate was significantly lower and her basal metabolic rate significantly higher. A noteworthy improvement for her in the HSF phase was virtual elimination of lifelong, severe hyperhidrosis. This has persisted now for 3.5 months. The male subject's BMR and BAT were not different in the two phases. However, during the HSF phase, he had a significantly lower heart rate, diastolic blood pressure, pain distribution, pain intensity, and mean intensity of hypothyroid symptoms. **Conclusions:** Both Cynomel and HSF were effective. HSF, however, appears to have provided additional improvements. The physiological equivalency of HSF to Cynomel for the female was calculated to be 1 capsule to 14.4 mcg and for the male was 1 capsule to 15 mcg.

Key Words. Basal metabolic rate ● Basal temperature ● Cynomel ● Cytomel ● Desiccated thyroid ● Hypo Support Formula ● RLC Labs ● Triiodothyronine

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Introduction

Dietary natural desiccated thyroid products have been available for purchase without a prescription in the U.S. since the 1994 Dietary Supplemental Health and Education Act.[1] The Act has enabled U.S. citizens to exercise considerable freedom in their choices of health care products, including dietary desiccated thyroid. This freedom has been extremely important to hypothyroid patients whose health has been adversely affected by the current conventional medical dictate that T_4 replacement is the only legitimate approach to thyroid hormone therapy.[25]

Despite the widespread use of dietary desiccated thyroid products, no studies appear to have been published in which researchers evaluated the efficacy of such products. The purpose of this study was to determine: (1) whether an organic dietary desiccated thyroid product (Hypo Support Formula[2] or HSF) was clinically effective compared to a synthetic T_3 product (Cynomel[3]); (2) the clinical equivalence of HSF to Cynomel; and (3) differences in clinical measurements while subjects took only HSF and only Cynomel.

Methods

Subjects. Two subjects took part in the study. One was a 49-year-old female with hypothyroidism, the other a 62-year-old male with partial peripheral resistance to thyroid hormone.

In 2006, the female subject had symptoms characteristic of hypothyroidism, a low basal body temperature, and the relaxation phase of her Achilles reflex was visibly slow. Because of her symptoms, she wanted to undergo a trial of thyroid hormone therapy.

In 2006, when she was 47-years-old, she underwent two basal metabolic rate (BMR) measurements. At the time, she was not taking exogenous thyroid hormone. On June 18, 2006, her BMR was 550 kcal/day. Her lean body weight (measured with 4-

electrode bioelectrical impedance) was high enough so that her predicted BMR (using the Sterling-Pasmore equation) was 807 kcal/day. Her measured BMR, then, was 32% lower than her BMR predicted by her lean body weight.

For her sex, age, height, and weight (using the Mifflin-St.Joer equation), her predicted BMR was 1115 kcal/day. Her measured BMR, therefore, was 51% lower than her predicted BMR using her sex, age, height, and weight.

The 308 kcal/day difference between the BMR predicted by her lean body weight and that predicted by her sex, age, height, and weight is unusual. In this case, the difference results from the subject having lower lean body weight than the average female of her age, height, and weight. Her lower lean body weight is evident in her slender body form, a physical feature she shares with a monozygotic sister.

The female subject's second BMR measurement was on September 29, 2006. Her measured BMR was 677 kcal/day. Her predicted BMR based on her lean body weight was 949 kcal/day. This BMR was 29% lower than that the BMR predicted by her lean body weight. The BMR predicted from her sex, age, height, and weight was 1120 kcal/day. Her measured BMR, then, was 40% lower than that predicted by her sex, age, height, and weight.

In metabolic clinical practice, if a patient has a low BMR and low lean body weight, it is appropriate for the patient to undergo a regimen of resistance exercise to increase his or her muscle and connective tissue mass. This is important because lean body weight is the strongest determinant of the BMR.[17-21] To determine whether resistance exercise, or more resistance exercise, is necessary for a patient, the lean body weight should be measured. The clinician should use the measurement in an equation such as the Sterling-Pasmore equation to obtain the predicted BMR by lean body weight. The patient's BMR should be measured with indirect calorimetry, and a calculation made to determine what percentage of the measure BMR is of the predicted BMR.

When this procedure was done for the female subject in 2006, she had enough lean body weight to have measured BMRs 29% higher on the first occasion and 32% higher on the second. It was clear from this outcome that low lean body weight was not the major mechanism of her low BMR, although perhaps a minor one. This was consistent with the fact that typically, she did resistance training at a gym seven days per week. She also was not restricting her calorie intake, which could have potentially lowered her measured BMR.[22] Because of these findings, she opted to increase her measured BMR by using Cynomel, starting with a single daily dose of 25 ì g.

The other subject, a 62-year-old male, had been stable on his optimal dose of synthetic T_3 for 23 years. He started treatment with Cytomel but for 8 years preceding this study, he had used Cynomel. His symptoms that were relieved by synthetic T_3 were intermittent suicidal depression, persistent cognitive dysfunction, and chronic pain referred from myofascial trigger points. After Synthroid and Jones desiccated thyroid failed to relieve his symptoms, Cytomel effectively relieved them. His effective dosage was 150 mcg.

His BMR, measured many times over the previous 5 years, was close to the predicted BMR by equations using both his lean body weight and his sex, age, height, and weight. As the Cynomel phase in Figure 2 shows, his measured BMR was closer to the BMR predicted by his lean body weight (green line with solid dots as predicted BMRs) and further away from the BMR predicted by his sex, age, height, and weight (brown line with square data points and yellow line with triangular data points).

Procedures. Upon waking from sleep and when comfortable with the temperature and bedding, each subject measured his or her basal metabolic rate with a hand-held indirect calorimeter (the MedGem®, Healthetech, Golden, Colorado). The subject then measured his or her basal axillary temperature of the left armpit with an electronic thermometer that gave a digital reading (Walgreens model VT-820W5T). The electronic thermometers were compared in a concurrent study to measurements with Galinstan-in-glass thermometers (Geratherm Medical AG, Fahrenheitstraße 1, D-98716 Geschwenda), which is equivalent to mercury thermometers. Measurements with the electronic and Galinstan thermometers strongly correlated and were highly consistent.[7] Each subject then took his or her basal pulse rate and blood pressure with an electronic sphygmomanometer (Omron Healthcare, Inc., Model HEM711-ACN, Bannockburn, IL.).

After arising from bed, the subjects measured the height and weight on a balance beam scale (Health-ometer, Continental Scale Corp., Bridgeview, IL), drank approximately two 8-ounce glasses of water, and then measured their body composition by 4-electrode bioelectrical impedance (Biodynamics® Model 310, Seattle, WA).

Next the subjects filled out three sets of evaluation forms: (1) a questionnaire with visual analog scales for 12 major symptoms characteristic of hypothyroidism;[6] (2) Zung's Self-rating Depression Scale (W.W.K. Zung © 1991); and (3) body drawings with 36 divisions for shading in the distribution of pain since the previous evaluation.[11]

After each evaluation, all measurements and scores were tabulated in an Excel spreadsheet in preparation for statistical analyses.

Study Design. An intrasubject replication study design (also termed a two-phase single-subject repeated measures design) was used.[8-16] The study actually involved three phases with repeated measurements in each, but comparisons were made only of the data from the first, the Cynomel phase, and the second, the HSF phase. The third phase was sandwiched between the Cynomel and the HSF phases. It was a transition phase during which the subjects progressively decreased their daily Cynomel intake and increased their HSF intake until their clinical measures were either acceptable or the same as in the Cynomel phase. For the female, the transition phase included 10 evaluations between November 8 and 24; for the male subject, the phase included 14 evaluations between November 1 and 25.

All phases occurred between October and December, 2008. In the first phase (the Cynomel-only phase), the female subject underwent 10 sets of measurements on different mornings between October 9 and November 5. The male subject underwent 12 sets of measurements between October 9 and 26. The mornings that the subjects chose to undergo evaluations were selected for convenience.

The subjects, both of whom were stable on their daily dosages of Cynomel[3], continued those dosages until all first-phase measurements were completed. The female subject's dose was 87.5 mcg and the male subject's dose was 150 mcg. Each took Cynomel on an empty stomach once per day.

As soon as each subject had stopped Cynomel altogether and was taking only HSF, the HSF phase began. During this phase, each subject underwent the same number of evaluations as in the Cynomel phase. The female subject underwent 10 evaluations between December 2 and 18, and the male subject 12 evaluations between November 26 and December 27.

After the subjects completed the HSF phase, they had electrocardiograms (ECGs).[15] The tracings were compared with ECGs performed before the study began. When the study began, the subjects filled out a sheet of visual analog scales containing common symptoms of thyrotoxicosis. The scores on the sheets were compared to subsequent sheets as indicators of possible symptoms of thyrotoxicosis.

Statistical Analyses. The t-test was used to test for differences between mean measurements. Levene's test for equality of variances was used to test for differences in the variance of measurements between the Cynomel and HSF phases. Bloom's probability table was used to statistically analyze any differences between Cynomel and HSF phases by the trend line method. The level of significance was set at $p \leq 0.05$. Statistical analyses were performed with SPSS for Windows® (SPSS, Inc., Chicago, IL), VassarStats: Website for Statistical Computation, and Microsoft® Excel 2002.

Results

Basal Metabolic Rate. The female subject's mean measured BMR during the Cynomel phase was significantly lower than in the HSF phase (828 ± 197 kcal/day vs 1034 ± 64 kcal/day, $p = 0.006$). Variances of the BMR measurements within each phase also differed (F = 12.668, $p = 0.002$).

Figure 1 contains the measured BMRs for the female subject. Each BMR along the blue trend line is represented by an empty circle. The difference in BMRs between the Cynomel phase (left half of the graph) and the HSF phase (right half of the graph) are visibly obvious, with higher measured BMRs in the HSF phase of the study. According to Bloom's probability table,[5] because in the Cynomel phase (left half of graph), 5 measured BMRs are above and 5 below the trend line, and 10 BMRs are included in the HSF phase (right side of graph), 9 measured BMRs above the trend line in the HSF phase constitutes a statistically significant increase of BMRs at the 0.05 level.

The male subject's mean measured BMR during the Cynomel phase did not significantly differ from that in the HSF phase (1830 ± 256 kcal/day vs 1905 ± 136 kcal/day, $p = 0.377$). Variances of the BMRs within reach phase also did not differ (F = 1.609, $p = 0.218$).

Figure 2 contains the male's measured BMRs (blue line with open circles representing each BMR). By Bloom's probability table,[5] with the baseline including 12 BMRs, and 5 below and 5 above the trend line for HSF-phase BMRs to be significantly different from those in the Cynomel phase. This criterion is not met. The lack of a significant difference is consistent with the lack of difference in the mean measured BMRs of the two phases.

Basal Axillary Temperatures. Both subjects were stable on Cynomel before this study, rarely experiencing mild symptoms characteristic of hypothyroidism. Despite this, both always had basal axillary temperatures below the lower end of the reference range reported by Barnes (97.8°F-to-98.2°F).[4]

Figure 1. Female Subjects' Measured BMRs & Predicted BMRs
(Cytomel phase: left half of graph; HSF phase: right half.)

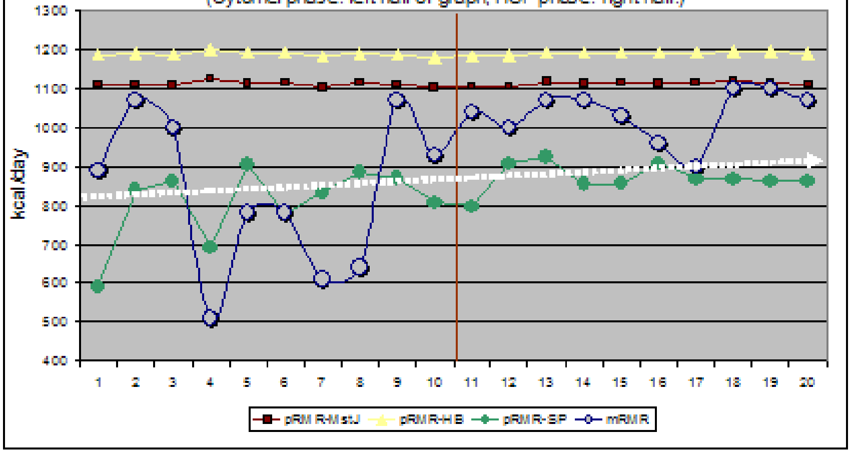


Figure 2. Male Subject's Measured BMRs & Predicted BMRs
(Cytomel phase: left half of graph; HSF phase: right half.)

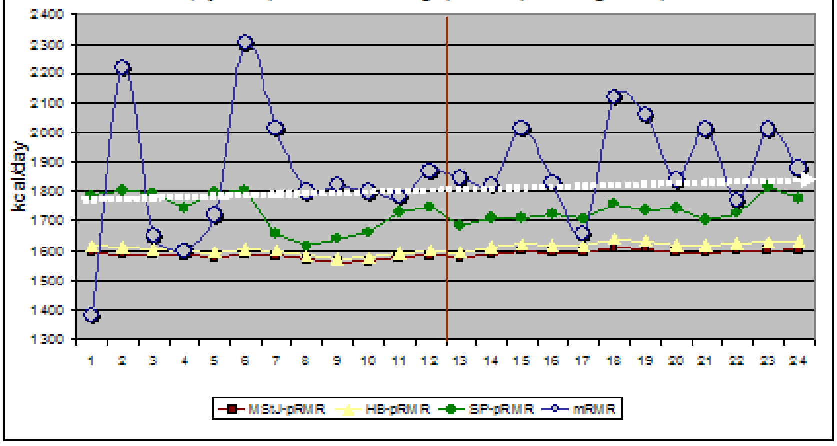
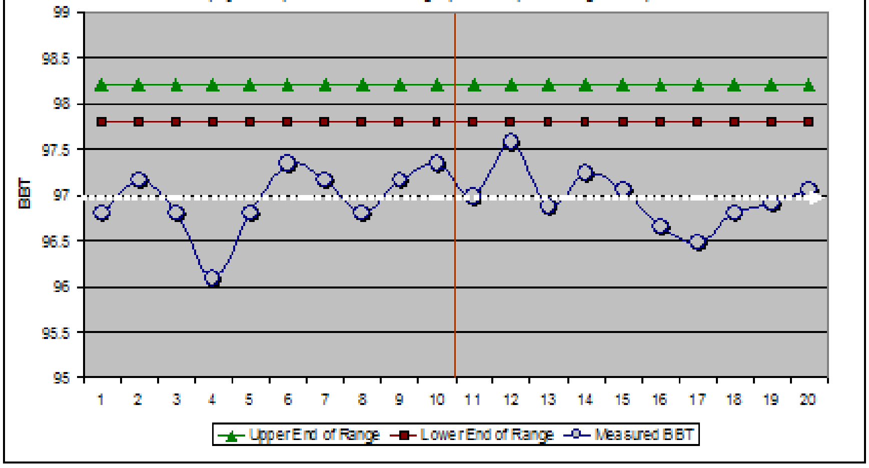


Figure 3. Female Subject's Basal Body Temperatures (BBT)
(Cytomel phase: left half of graph; HSF phase: right half.)



trend line, 9 measured BMRs in the HSF phase (right half of graph) would have to be above or below the

In the Cynomel phase (left half of graph in Figure 3), the female's mean basal axillary temperature was 96.944 ± 0.378°F. During the HSF phase, the mean temperature was 96.960 ± 0.303°F. The mean temperatures in the two phases did not significantly differ, nor were their variances significantly different.

Figures 3 contains the female's basal temperature measurements represented as open circles on the blue line. Using the probability table of Bloom,[5] with 10 measurements in the Cynomel phase (left half of graph), with 5 above and 5 below the tend line, 9 data points would have to be above or below the trend line in the HSF phase (right half of the graph) for her temperature to have significantly changed. This criterion is not met, so the subject's temperatures in the two phases were not significantly different.

The female subject's mean temperature in September 2006, taken 20 times, was significantly lower than her mean temperature in both the Cynomel phase (96.118 ± 0.567 vs 96.9440 ± 0.378, p = 0.001) and HSF phase (96.118 ± 0.567 vs 96.959 ± 0.303, p = 0.001). When she was taking 25 mcg of Cynomel in September 2006, then, her temperature was significantly lower than when she was taking 87.5 mcg of Cynomel and when she was taking 6 capsules of HSF. Her mean temperatures during the Cynomel phase of the study, however, did not significantly differ from those in the HSF phase.

The male subject's mean temperature was 96.778 ± 0.673.°F during the Cynomel phase and 96.914 ± 0.548.°F during the HSF phase. These mean temperatures did not significantly differ, nor did the variances of the two sets of temperature measures.

Despite the male subject's use of 150 mcg of synthetic T_3, his temperature was low throughout his 23 years of using Cytomel and Cynomel, usually within the range of 96.5 to 97.0°F. His mean temperature while on HSF alone remained virtually the same.

Figure 4 contains the male's basal temperatures. Using Bloom's probability table,[5] with 12 measurements in the Cynomel phase and 5 of the BMRs above and 5 below the trend line, 10 BMRs in the HSF phase would have to be above or below the trend line for the BMRs to significantly differ from those in the Cynomel phase. That criterion is not met, so the BMRs in the two phases do not significantly differ.

Basal Heart Rates. A t-test showed that the female subject's mean basal heart rate was significantly lower during the HSF phase than in the Cynomel phase (62.50 ± 4.04 bpm vs 68.35 ± 5.11 bpm, p = 0.011). Bloom's probability table[5] also shows a significantly lower basal heart rate in the HSF phase. With 10 BHR measurements in the Cynomel phase (left half of the graph), and 4 BHRs above and 4 below the trend line, then 8 BHRs would have to be above or below the trend line in the HSF phase (right half of the graph) for the BHRs in the two phases to significantly differ. This criterion is met.

The female subject's mean systolic and diastolic pressures during Cynomel and HSF phases did not significantly differ.

The male's mean BHR was also significantly lower in the HSF phase than in the Cynomel phase (72.96 ± 8.24 vs 81.79 ± 7.51, p = 0.012). Bloom's probability table[5] also shows a significantly lower basal heart rate in the HSF phase: with 12 BHRs in the Cynomel phase (left side of graph), and 5 of these above and 5 below the trend line, then in the HSF phase (right side of graph), 9 BHRs would have to be below the trend line for the HSF-phase BHRs to be significantly lower at the 0.05 level. In fact, 10 BHRs were below the trend line. His heart rate was therefore significantly lower in the HSF phase.

The male subject's systolic pressure in the HSF phase was lower than in the Cynomel phase but did not quite reach statistical significance (123.08 ± 7.75 vs 129.27 ± 8.18, p = 0.07). His diastolic pressure, however, was significantly lower in the HSF phase than in the Cynomel phase (71.4167 ± 4.35 vs 77.14 ± 5.43, p = 01).

Weight and Fat Weight. Between the Cynomel and HSF phases, the female subject had no significant changes in weight, percentage body fat, fat or lean weight. For the male subject, however, weight was significantly higher during the HSF phase than in the Cynomel phase (174.93 ± 1.86 lbs vs 170.73 ± 2.13 lbs, p < 0.0001), and his fat weight was significantly higher during the HSF phase (49.24 ± 1.87 vs 45.33 ± 3.71, p = 0.005). His weight, or lean weight. For the male subject, however, weight was significantly higher during the HSF phase than in the Cynomel phase (174.93 ± 1.86 lbs vs 170.73 ± 2.13 lbs, p < 0.0001), and his fat weight was significantly higher during the HSF phase (49.24 ± 1.87 vs 45.33 ± 3.71, p = 0.005). His percentage body fat, however, was not significantly different in the two phases.

Mean Symptoms Intensity. For the female subject, the mean intensity of her symptoms characteristic of hypothyroidism did not significantly differ

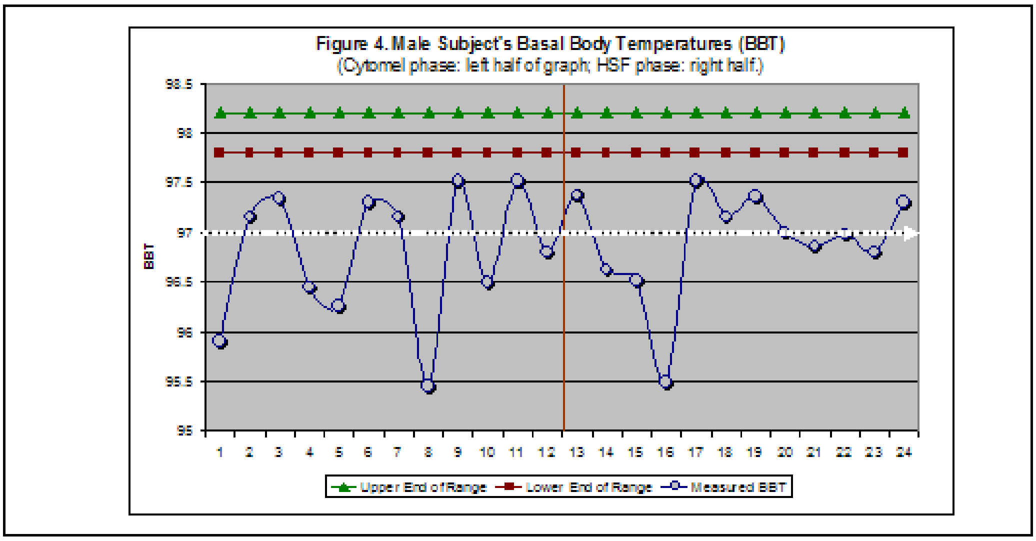


Figure 4. Male Subject's Basal Body Temperatures (BBT)
(Cytomel phase: left half of graph; HSF phase: right half.)

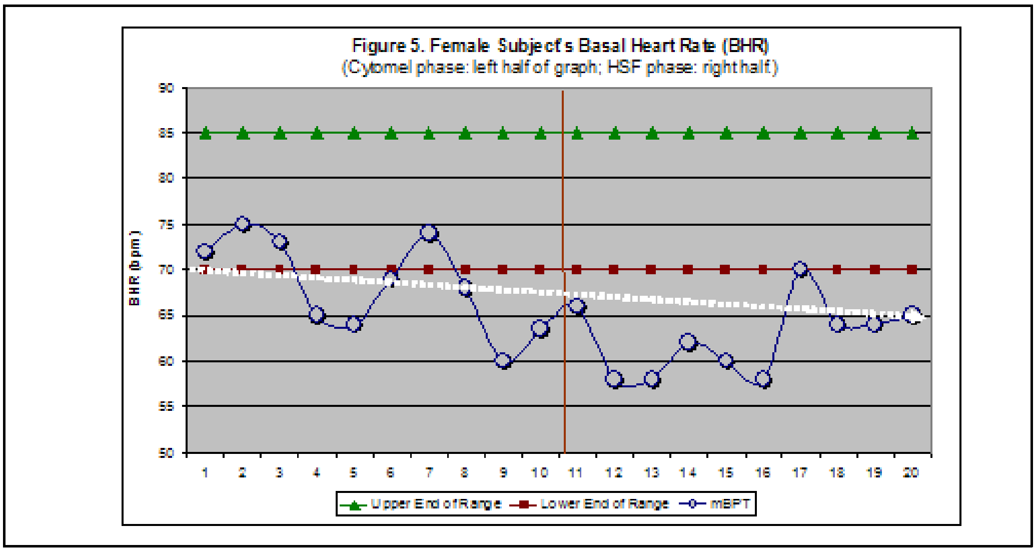


Figure 5. Female Subject's Basal Heart Rate (BHR)
(Cytomel phase: left half of graph; HSF phase: right half.)

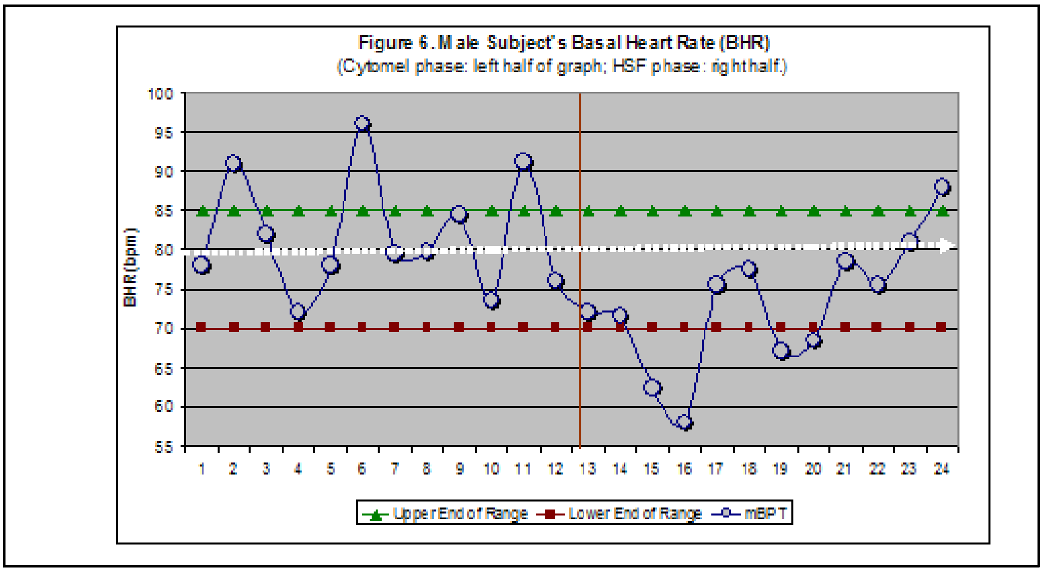


Figure 6. Male Subject's Basal Heart Rate (BHR)
(Cytomel phase: left half of graph; HSF phase: right half.)

in the two phases. The mean intensity in the Cynomel phase was 3.68 (range from 0-to-10), and during the HSF phase was 2.68. Subjectively, however, she reported that as a global assessment, she felt better in the HSF phase.

In both phases, the male subject's mean symptoms intensity was low. However, the mean intensity of his symptoms was significantly lower in the HSF phase than in the Cynomel phase (1.09 ± 0.64 vs 2.18 ± 0.53, $p = 0.001$).

Zung's Self-rating Scale. During the Cynomel phase, the female subject had mild depression according to her mean Zung's score. In the HSF phase, however, her mean Zung's score was enough lower that it was significantly different from the mean scores in the Cynomel phase (1.67 ± 0.87 vs 1.00 ± 0.00, $p = 0.05$). The subject reported that the depression during the Cynomel phase was situational and uncharacteristic for her throughout her previous life, including her two years of Cynomel use.

For the male subject, the mean Zung's scores showed no depression in either of the two phases.

Pain Distribution. The female subject's pain distribution was not significantly different in the two phases. In the Cynomel phase, her mean pain distribution was 6.06% of 36 body divisions; in the HSF phase, the distribution was 5.81% of the 36 divisions.

The male subject's pain distribution was small in both phases, but it was highly significantly smaller in the HSF phase than in the Cynomel phase (0.22 ± 0.08 vs 1.98 ± 0.71, $p = 0.00003$).

Pain Intensity. The female subject's pain intensity did not significantly differ between the Cynomel and HSF phases. The male subject's pain intensity, however, was significantly lower in the HSF phase than in the Cynomel phase (0.22 ± 0.33 vs 1.68 ± 1.42, $p = 0.007$).

Discussion

Results of the clinical measures used in this study indicate that both Cynomel and HSF were effective. However, HSF provided some improvements in the subjects' clinical status that Cynomel did not provide. No symptoms of thyroid hormone overstimulation or ECG/EKG abnormalities were associated with the subjects' use of Cynomel or HSF.

Body Composition. Evaluation of the composition of an individual patient's body (a type of "clinico-anthropometric" analysis) is often essential to accurately diagnosing a disorder that afflicts him or her.[23] Similarly, a clinico-anthropometric analysis is often essential to finding a plausible explanation for an unexpected therapeutic effect. This is true for the female subject in this study: Her increased mean measured BMR when taking HSF was unexpected, and a likely mechanism for the increase becomes clear only through consideration of her body composition.

For two years prior to this study, the female subject had been free from symptoms characteristic of hypothyroidism by taking 87.5 mcg of Cynomel per day. Figure 1 shows visually that Cynomel maintained her BMRs closer to BMRs predicted by her lean body weight (green line in left half of the graph with solid dots as data points), and considerably lower than BMRs predicted by her sex, age, height, and weight (brown line in left half of graph with squares as data points and green line with triangles as data points). Her measured BMR being closer to her predicted BMR by lean body weight appears to have resulted from her ectomorphic body form. (The ectomorphic form is characterized by the relative prominence of structures derived from the embryonic ectoderm.[41][42]) The subject is more slender than other women of her age, height, and weight, as is her identical twin sister.

In the HSF phase, her BMRs were closer to those predicted by her sex, age, height, and weight, and further away from those predicted by her lean body weight. In looking for a plausible mechanism of her increased BMRs in the HSF phase (represented by data points 11 through 20 on the right side of the graph in Figure 1), lean body weight and thyroid hormone regulation of cell function are the two most important considerations. The reason is that among the determinants the BMR,[17-21] lean body weight is the most influential thyroid hormone is the second.

Her lean body weight was not higher in the HSF phase, and therefore could not have been the factor that raised her measured BMRs. In the U.S., the exact thyroid hormone content of dietary desiccated thyroid hormone products are not known. The FDA, however, does require that all but trace amounts of the T_4 be removed from the products. It is within the realm of possibility that thyroid hormones other than T_4 increased the subject's BMRs in the HSF phase.

It is also possible that one or more ingredients in the HSF capsules other than thyroid hormone increased her intracellular rate of oxidative metabolism. Such an increase in turn would have raised her oxygen consumption in the vegetative state during which she measured her BMR with a handheld calorimeter.

One would expect an increased rate of oxidative metabolism to increase the subject's calorie expenditure. This expectation is reasonable in that an increased BMR by definition is a higher calculated 24-

hour basal energy expenditure, which in turn is computed from oxygen consumption in a basal state. The increased energy expenditure is expected to change the body composition of the subject unless she also increases her calorie intake to compensate for the increased expenditure. However, the subject had virtually the same calorie consumption in the Cynomel and HSF phases. Because of this, one would expect that the subject would have had a lower weight and body fat measures during the HSF phase. This was not the case, however. The author knows of no explanation for this discrepancy.

In contrast to the female subject, the male has a mesomorphic body form; that is, the form is characterized by the prominence of structures derived from the embryonic mesoderm.[41][42] This appears to account for his BMRs, measured many times over the previous 5 years, most often being close to the BMR predicted from his lean body weight, and further away from the BMR predicted by his sex, age, height, and weight. This indicates that he had more lean body weight than the average male of his age, height, and weight. Figure 2 shows his measured BMRs (blue line with open circles in both halves of the graph) was generally closer to the BMRs predicted by his lean body weight (green line with closed dots) than they were to the BMRs predicted by his sex, age, height, and weight (brown line with square data points and yellow line with triangular data points).

Sympathetic Nervous System Activity. Several findings in this study during the subjects' HSF phases could be due to reduced sympathetic nervous system activity. In turn, theoretically, the putative reduced sympathetic activity could be due to decreased regulation of transcription of the adrenergic genes by thyroid hormone, resulting in a reduced number of stimulatory â-adrenergic receptors and an increase number of inhibitory á-adrenergic receptors.[40,pp.341-377] This mechanism could possibly account for five HSF-phase findings: for the female and male, reduced heart rates, subjective calmness, and a lower spread of BMR values around mean BMR values; for the female alone, improved hyperhidrosis; and for the male alone, lower blood pressure and increased weight.

Heart rate and blood pressure. Both subjects had significantly lower basal heart rates in the HSF phase. The female subject's systolic and diastolic pressures were not significantly different in the Cynomel and HSF phases. The male had reduced systolic pressure that approached statistical significance, and diastolic pressure that was significantly lower.

Hyperhidrosis. The virtual elimination of the female subject's life-long hyperhidrosis in the HSF phase and afterward might have involved any of several possible mechanisms.[26][27] One is a reduction in sympathetic activity, indicated by studies that show improved hyperhidrosis following surgical applications of clips above and below various thoracic sympathetic ganglia[28][29] and occasional effective adrenergic receptor blockade.[27]

Lower spread of BMRs from the mean BMR values. The lower variance of measured BMRs for the female subject in the HSF phase might also have resulted from lower sympathetic nervous system activity. The lower variance was significant (F = 12.668, $p = 0.002$). Two other descriptive data calculations show a wider distribution of BMRs during the Cynomel phase. In that phase, the range (the difference between lowest and highest BMRs) of BMR measurements (the difference between the minimum and maximum BMR) was 630 kcal/day. In the HSF phase, the range was only 230 kcal/day. And the respective standard deviations in the Cynomel and HSF phases were 213.58 kcal/day and 67.26 kcal/day, showing that the spread of BMR measurements around the mean were larger in the Cynomel phase.

For the male subject, the variances of BMRs did not significantly differ in the two phases (F = 1.609, $p = 0.218$). However, in the Cynomel phase, the range of BMR measurements was 925 kcal/day compared to only 460 kcal/day in the HSF phase. Similarly, in the Cynomel phase, the standard deviation was 255.4596 kcal/day compared to 135.979 kcal/day in the HSF phase.

For both subjects, then, BMRs in the HSF phase were less widely distributed than in the Cynomel phase. This may have resulted from lower sympathetic nervous system responsiveness in the HSF phase.

Subjective calmness. Toward the end of the transition phase, just before stopping Cynomel altogether and reaching their apparent optimal dosages of HSF, the subjects reported feeling a persistent and distinct subjective sense of calm. The female reported feeling "a more steady, stabilized sense of well-being, and less warmth after eating" (postprandial thermogensis). The male subject recorded feeling "calmer, less anxious except situationally, and mildly sedate without sleepiness." Both subjects recorded that these subjective feelings had persisted long enough so that they appeared to be associated with the HSF.

Weight. The significant increase in the male subject's total weight and fat weight could be argued to have resulted from HSF decreasing his sympathetic activity. Decreased sympathetic nervous system activity, with consequently decreased secretion of adrenaline and noradrenaline, could have decreased the mobilization of fatty acids from adipose tissue. The resulting higher triglyceride content of the adipose tissues could account for weight gain and higher fat measurements. But this mechanism is unlikely. If this mechanism was operative in the male subject, it is likely that it would also have been operative in the female subject. However, she did not have a significant increase in her total weight or fat weight. In addition, the male subject, who has a lifelong commitment to fitness, was uncharacteristically sedentary through the study due to compelling work responsibilities. It is far more likely, then, that his weight gain of 4.2 lbs resulted from reduced calorie expenditure from a lower than usual level of physical activity.

If HSF were less potent than Cynomel in maintaining the â- and á-adrenergic balance expected from effective thyroid hormone therapy, then reduced sympathetically-mediated phenomena would be expected. These would include several found in the HSF phase of the study: reduced mean heart rate, improved hyperhidrosis, reduced diastolic pressure, and the subjective sense of calm. Other findings in the HSF phase, however, are inconsistent with reduced sympathetic activity. These are the lack of a significant difference between the male's mean BMRs in the Cynomel and HSF phases, and the increase in the female's mean BMR during the HSF phase. At the moment, the seemingly contradictory findings in regard to sympathetic function are inexplicable to the author.

Pain Reduction. The female subject's pain distribution and intensity were not significantly different in the two phases. In that her metabolic and clinical status were actually improved in the HSF phase, her pain most likely has a mechanism unrelated to her thyroid hormone status.

The male subject's lower pain distribution and intensity in the HSF phase constituted improved clinical status for him. Thyroid hormone therapy can reduce or alleviate pain by lowering substance P, a compound that amplifies neural signals that give rise to the perception of pain. Thyroid hormone normally inhibits the synthesis and secretion of substance P in many CNS cells. It does so by repressing transcription of the preprotachykinin-A gene. Preprotachykinin-A is the precursor of substance P and its cognate substance P receptor.[31,32] In studies, lowering thyroid hormone levels by thyroidectomy increased the substance P level in astrocytes,[32] anterior pituitary,[33,34,35] many brain nuclei,[38] and, most relevant to pain, the dorsal horns of the lumbar spinal cord. The increase in dorsal horn substance P was extreme (100%)[36,37] as in FMS patients.[30] Thyroid hormone treatment lowered the substance P level in the anterior pituitary,[34] brain nuclei,[39] and the dorsal horns.[37] Administering excessive amounts of thyroid hormone reduced substance P to subnormal levels.[35] Reduction of the substance P level is probably the mechanism for the relief of the chronic pain of fibromyalgia when patients are effectively treated with thyroid hormone therapy.[40,43-50]

Reduced substance P, however, seems like an unlikely mechanism of the male subjects improved pain measures in the HSF phase. Synthetic T_3 had effectively reduced his chronic myofascial pain and other somatic discomforts for years, the symptoms returning only during times when he had purchased subpotent Cytomel.

The pain reducing effect for him during the HSF phase may not be related to the thyroid hormone. Instead, the tyrosine in HSF may have had an analgesic effect. This is possible because tyrosine is the NH_2 terminal that is absolutely necessary for enkephalins to exert analgesic effects when they bind to opiate receptors.[24]

Effectiveness of HSF and Cynomel. The male subject's mean BMR did not differ between the Cynomel and HSF phases. The female subject's mean BMR during the HSF phase was significantly higher than in the Cynomel phase. However, she was not hypermetabolic in the HSF phase: her BMRs in this phase were between the BMRs predicted from her lean body weight and and those predicted from her sex, age, height, and weight (see Figure 1). In addition, she had no signs or symptoms characteristic of thyrotoxicosis, did not have hyperreflexia, she was satisfied subjectively with the effects of 6 capsules of HSF, and her measurements overall indicate a somewhat improved clinical status.

Safety. The subjects had no symptoms of thyrotoxicosis in any phase of the study. This was partly determined by comparing the intensity ratings of symptoms of thyrotoxicosis on visual analog scales that they filled out before the study and at intervals during the two phases. Neither subject had hyperreflexia. After the study, their ECGs/EKG tracings were no different from those performed before the study began. The thyrotoxicity symptom assessment, normal Achilles reflexes, and unchanged normal ECGs/EKGs indicate that neither Cynomel nor HSF in the dosages the subjects used had adverse effects.

Limitations. This study was unblinded, which raises the possibility of observer bias. However, the number of repeated measurements during the two analyzed phases diminishes the likelihood that the outcome was influenced by subtle biases.

In general, the clinical research community nowadays considers the only useful study method to be the randomized double-blind placebo-controlled design. An argument that the design of the study reported here is limited because it is not the randomized method is not truly a limitation of the study; rather, it is a limitation of the appreciation of the rich and fruitful use of study designs other than the randomized double-blind placebo-control procedure.

The single-subject A-B repeated measures design used in this study has merits lacking in the randomized design. For example, the subject who serves as the patient in one study phase also serves as the control in another. This eliminates the need for randomization in that the patient and the control could not be more perfectly matched. Also, repeated measures under systematically varied conditions not only provides data for traditional group statistical analyses, but also allows for clear visual assessment of functional relationships between independent and dependent variables.

Conclusion

In this study, both Cynomel and HSF, a dietary organic desiccated thyroid product, were physiologically effective. HSF, however, appears to have provided some improvements in the subjects' physiological status that Cynomel did not provide. The female subject's axillary temperatures did not differ in the two phases. In the HSF phase, however, her heart rate was significantly lower and her mean basal metabolic rate was significantly higher. A noteworthy benefit for her was the virtual elimination of previous life-long hyperhidrosis of her palms and soles; the reduced perspiration at this time has lasted 3.5 months.

The male subject's basal metabolic rates and basal axillary temperatures did not differ in the Cynomel and HSF phases. However, in the HSF phase, five measures were significantly lower: his heart rate, diastolic blood pressure, pain distribution, pain intensity, and mean hypothyroid symptoms intensity.

The physiological equivalence of HSF to Cynomel was calculated from the patients' dosages of HSF in their HSF phases that maintained measurements equivalent to or better than those in the Cynomel phase. The physiological equivalence of HSF to Cynomel was 1 capsule of HSF to 14.58 mcg of Cynomel for the female subject, and 1 capsule to 15 mcg for the male.

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*Director of Research, Fibromyalgia Research Foundation

Contact: drlowe@FibromyalgiaResearch.org, drlowe@drlowe.com

Abstract. Broda Barnes' publications have influenced many clinicians to use the basal body temperature in diagnosing hypothyroidism and determining patients' dosages of thyroid hormone. Barnes recommended that patients use inexpensive and reliable portable mercury-in-glass thermometers. These are no longer available, so many clinicians now recommend that patients use either electronic thermometers or Galinstan-in-glass thermometers that are mercury-free. Researchers have compared the temperature readings of mercury thermometers with both those of electronic and Galinstan thermometers. However, no studies could be found in which measurements with electronic thermometers were compared to those of Galinstan instruments. The purpose of this study was to compare measurements with these two types of thermometers. **Methods**: To avoid variations between subjects and anatomical sites, measurements were taken by one subject using the left axilla. The subject took 10 measurements simultaneously with an electronic and a Galinstan thermometer. Two electronic thermometers (E-1 and E-2) were compared separately with two Galinstan thermometers (G-1 and G-2) so that four sets of 10 paired measurements were taken. **Results**: The correlation between measurements with the four pairings of electronic and Galinstan thermometers was strong and statistically significant (E-1 & G-1, $r = 0.985 \pm 0.674$ vs 0.638, $p < 0.0001$. E-1 & G-2, $r = 0.945 \pm 0.302$ vs 0.272, $p < 0.0001$. E-2 & G-1, $r = 0.980 \pm 0.587$ vs 0.627, $p < 0.0001$. E-2 & G-2, $r = 0.976 \pm 0.671$ vs 0.529, $p < 0.0001$.). Also, differences between mean measurements using pairs of thermometers were not statistically significant (E-1 & G-1, 97.266 ± 0.674°F vs 97.190 ± 0.638°F, $p = 0.798$. E-1 & G-2, 97.327 ± 0.302°F vs 97.193 ± 0.272°F, $p = 0.309$. E-2 & G-1, 97.016 ± 0.587°F vs 97.107 ± 0.627°F, $p = 0.743$. E-2 & G-2, 96.638 ± 0.671°F vs 96.841 ± 0.529°F, $p = 0.462$. For metric values, see Table 1). **Conclusion**: Readings using electronic and Galinstan thermometers from the same axilla of one subject were consistent enough to be of reliable clinical use.

Keywords • Analog thermometer • Axillary temperature • Digital thermometer • Electronic thermometer • Galinstan thermometer • Mercury thermometer

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Axillary Electronic and Galinstan Thermometer Measurements: A Comparison of Their Consistency

Dr. John C. Lowe*

*Director of Research, Fibromyalgia Research Foundation
Contact: Dr. John C. Lowe drlowe@drlowe.com

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Abstract. Broda Barnes' publications have influenced many clinicians to use the basal body temperature in diagnosing hypothyroidism and determining patients' dosages of thyroid hormone. Barnes recommended that patients use inexpensive and reliable portable mercury-in-glass thermometers. These are no longer available, so many clinicians now recommend that patients use either electronic thermometers or Galinstan-in-glass thermometers that are mercury-free. Researchers have compared the temperature readings of mercury thermometers with both those of electronic and Galinstan thermometers. However, no studies could be found in which measurements with electronic thermometers were compared to those of Galinstan instruments. The purpose of this study was to compare measurements with these two types of thermometers.

Methods. To avoid variations between subjects and anatomical sites, measurements were taken by one subject using the left axilla. The subject took 10 measurements simultaneously with an electronic and a Galinstan thermometer. Two electronic thermometers (E-1 and E-2) were compared separately with two Galinstan thermometers (G-1 and G-2) so that four sets of 10 paired measurements were taken.

Results. The correlation between measurements with the four pairings of electronic and Galinstan thermometers was strong and statistically significant (E-1 & G-1, $r = 0.985 \pm 0.674$ vs 0.638, $p < 0.0001$. E-1 & G-2, $r = 0.945 \pm 0.302$ vs 0.272, $p < 0.0001$. E-2 & G-1, $r = 0.980 \pm 0.587$ vs 0.627, $p < 0.0001$. E-2 & G-2, $r = 0.976 \pm 0.671$ vs 0.529, $p < 0.0001$.). Also, differences between mean measurements using pairs of thermometers were not statistically significant (E-1 & G-1, 97.266 ± 0.674 F vs 97.190 ± 0.638 F, $p = 0.798$. E-1 & G-2, 97.327 ± 0.302 F vs 97.193 ± 0.272 F, $p = 0.309$. E-2 & G-1, 97.016 ± 0.587 F vs 97.107 ± 0.627 F, $p = 0.743$. E-2 & G-2, 96.638 ± 0.671 F vs 96.841 ± 0.529 F, $p = 0.462$. For metric values, see Table 1).

Conclusion. Readings using electronic and Galinstan thermometers from the same axilla of one subject were consistent enough to be of reliable clinical use.

Keywords. Analog thermometer • Axillary temperature • Digital thermometer • Electronic thermometer • Galinstan thermometer • Mercury thermometer

Introduction

Mercury-in-glass thermometers have long been in clinical use, so long that some researchers have referred to them as "standard mercury thermometers,[1] the "standard clinical thermometer,[10,p.1550] and the "gold standard. [11,p.1]

Because of the toxicity of mercury, the FDA and similar agencies in France and Scandinavia have banned mercury thermometers. Two other types of thermometers, electronic and Galinstan-containing instruments, now substitute for mercury-containing thermometers.

The "Geratherm [4] brand Galinstan thermometer is a traditional "shake-down glass analog device. Galinstan is a fluid substitute for mercury. It is a mixture of three metallic elements: gallium, indium, and tin.[5] The mixture is a eutectic alloy, meaning it is highly convertible from solid to liquid state because its melting point is lower than that of other mixtures of the same ingredients.

Electronic digital thermometers, powered by a button battery, are now in widespread use in the United States. An advantage of the instrument is the short time needed to obtain temperature measurements. Some patients, however, have expressed concern over wide variations in their armpit temperature readings with electronic thermometers. Some clinicians also doubt the reliability of temperature measurements taken with electronic thermometers. For example, a physician wrote: “Currently, mercury thermometers are unavailable and I recommend one with gallium called Geratherm. *(Warning: Do not use a digital thermometer for the results may not be accurate.)*’ [7] [Italics mine.] On the other hand, some companies have promoted electronic thermometers as more accurate than mercury thermometers.[2][3]

Several research groups have reported comparisons of temperature measurements using electronic and mercury thermometers.[1][8][9][10] Davies et al.[8] compared the two types of thermometers in a hospital ward. They wrote, “Both laboratory and clinical studies show that there is no significant difference in the average accuracy of the two types of thermometers. They stated, however, that temperature readings with electronic thermometers had greater fluctuation. “In clinical studies, they wrote, “between 9 and 23% of repeated measurements using an electronic thermometer differ by 0.5°C or more, whilst the corresponding range for mercury thermometers is 0-6%.

Jensen et al.[9] compared measurements with mercury thermometers to electronic thermometers in a hospital setting. Unlike the finding of Davies et al.,[8] Jensen et al. reported that electronic measurements were most accurate.[9]

Shanks et al. studied the accuracy of electronic thermometers.[1] Using 20 hospital inpatients as subjects, they compared measurements using electronic thermometers with those of standard mercury thermometers. They compared two brands of electronic thermometers with the mercury thermometer. Subjects put all three thermometers under their tongues simultaneously. The researchers found no significant difference between the measurements of the three thermometers. The average difference between the pairs of thermometers was 0.07 F (0.026 C).

Table 1. Insignificant differences between the mean measurements with four sets of electronic and Galinstan thermometers.

Thermometers compared	Number*	Means and SD of thermometer measurements	Differences between means and SDs	P value
Electronic-1 & Galinstan-1	10	97.266 ± 0.674 F vs 97.190 ± 0.638 F (36.259 ± 0.374 C vs 36.217 ± 0.354 C)	0.076 ± 0.036 F (0.042 ± 0.020 C)	0.798
Electronic-1 & Galinstan-2	10	97.327 ± 0.302 F vs 97.193 ± 0.272 F (36.293 ± 0.168 C vs 36.218 ± 0.151 C)	0.134 ± 0.030 F (0.074 ± 0.017 C)	0.309
Electronic-2 & Galinstan-1	10	97.016 ± 0.587 F vs 97.107 ± 0.627 F (36.120 ± 0.326 C vs 36.171 ± 0.348 C)	0.091 ± 0.040 F (0.050 ± 0.022 C)	0.743
Electronic-2 & Galinstan-2	10	96.638 ± 0.671 F vs 96.841 ± 0.529 F (35.910 ± 0.373 C vs 36.023 ± 0.294 C)	0.203 ± 0.142 F (0.113 ± 0.079 C)	0.462

* of paired measurements.

To the author’s knowledge, no one has reported a comparative study of the consistency of temperature readings with electronic and Galinstan thermometers. One purpose of this study was to fill this information gap in the field of thermometry. A corollary purpose was to determine whether measurements of the axillary temperature, using one armpit of one subject, would be consistent enough with the two types of thermometers to be of reliable clinical use.

Methods

Single Subject

So that intersubject variability was not an issue, only one subject participated in the study. The purpose was to quantify the consistency of temperature measurements by different types of thermometers;

this purpose was best served by avoiding variability in measurements due to different anatomical sites. Because of this, the subject's left axilla was selected as the single anatomic site at which to obtain measurements. Temperature measurements were taken simultaneously with two thermometers, one electronic thermometer and one Galinstan thermometer. The subject took some basal temperature measurements, but most were taken while the subject was sitting at rest.

Instruments

Temperature measurements were made with two Geratherm (Geratherm-1 and Geratherm-2) thermometers and two inexpensive model VT-820W5T Walgreens electronic thermometers (electronic-1 and electronic-2). Temperature readings of each of the Geratherm thermometers were compared with those of each of the electronic thermometers (see Table 1 for the raw data).

Procedure

The subject's left axilla was the site of all measurements. The protocol followed was that of using more than one thermometer simultaneously, as used in other studies comparing different instruments.[1][11]

Statistical Analysis

Data sets were compared and analyzed for variance by the Pearson product-moment correlation coefficient, by standard deviations, and by mean differences. Means of the measurements with paired thermometers were analyzed by t-tests. The level of significance was set at p 0.05. SPSS for Windows (SPSS, Inc., Chicago, IL), VassarStats: Website for Statistical Computation, and Microsoft Excel 2002 were used for statistical analyses.

Results

More measurements with electronic thermometers were outside two standard deviations from the mean measurements. Two readings with electronic-1 were below two standard deviations, and one reading with electronic-2 was below two standard deviations.

Table 2. Correlations between the measurements with four sets of electronic and Galinstan thermometers.

Thermometers compared	Number*	Pearson r	SD	Significance (2-tailed)
Electronic-1 & Galinstan-1	10	0.985	0.674 vs 0.638	< 0.0001
Electronic-1 & Galinstan-2	10	0.945	0.302 vs 0.272	< 0.0001
Electronic-2 & Galinstan-1	10	0.980	0.587 vs 0.627	< 0.0001
Electronic-2 & Galinstan-2	10	0.976	0.671 vs 0.529	< 0.0001

* of paired measurements.

One reading with Galinstan-2 was more than two standard deviations below the mean. All readings with Galinstan-1 were within two standard deviations.

The mean measurement with electronic thermometers (97.062 F; 36.146 C, ± 0.6201) closely correlated with the mean measurement with Galinstan thermometers (97.083 F; 36.157 C, ± 0.5362). The Pearson correlation coefficient of the two sets of measurements was high and positive ($r = 0.956, p < 0.0001$)

Levene's test for equality of variances showed that the variances of the measurements with paired thermometers were not significantly different. Because of this, t-tests for independent means with equal variances were used to test for differences between the mean measurements. The p values in Table 1 show that none of the mean measurements with paired thermometers were significantly different.

Table 1 also shows the differences between the means and standard deviations of temperature readings with paired measurements. The smallest difference was between the electronic-1 thermometer and the Galinstan-1 instrument. The largest difference was between the electronic-2 and Galinstan-2 thermometers. However, the differences were not statistically significant.

Table 3 shows the mean standard deviations for the two sets of temperature measurements with each thermometer, and those for the combined standard deviations for the two thermometers for each type of instrument. The mean standard deviation of electronic-1 was relatively low and that of electronic-2 was relatively high, while that of Galinstan-2 was relatively low and Galinstan-1 relatively high.

To show the variability of mean differences for all paired thermometers combined, a scatter plot was formulated in Figure 1. Figure 2 shows the mean differences for the four pairs of thermometers. In a study by Smith comparing mercury and Galinstan thermometers,[11,p.7] the mean difference between axillary temperatures by the two types of thermometers was 0.253 F (0.141 C). This is a lower difference than the 0.36 F (0.2 C) demarcation for including thermometers in several clinical studies with humans.[20][21][22][23] In this study, mean differences between axillary temperature measurements with different thermometers were less than in the Smith study. The combined mean difference for all paired thermometers was 0.126 F (0.070 C). The mean difference with E1 and G1 was 0.076 F (0.042 C), with E1 and G2 was 0.134 F (0.074 C), with E2 and G1 was 0.091 F (0.051 C), and with E2 and G2 was 0.203 F (0.113 C).

Table 3. Standard deviations for individual thermometers and mean standard deviations for combinations of thermometers.*

E1	E2	G1	G2	E1 & E2	G1 & G2	E1 & G2	E2 & G1
0.510	0.643	0.617	0.447	0.620	0.536	0.494	0.643

*(E1) Electronic-1. (E2) Electronic-2, (G1) Galinstan-1, (G2) Galinstan-2, (E1 & E2) Electronic-1 & -2, (G1 &G2) Galinstan-1 & -2, (E1 & G2) Electronic-1 & Galinstan-2, (E2 & G1) Electronic-2 & Galinstan-1.

The 95% confidence interval for difference scores was 0.152 F to 0.304 F. By comparison, the 95% confidence interval for axillary temperatures in the Smith study was 0.167 F to 0.339 F. The assumption of a normal distribution, however, is dubious, considering the skewed histogram of the difference scores (-1.807).[13][25]

Discussion

Some clinicians have reported that electronic thermometers are not as accurate as Galinstan thermometers,[7] and some companies that market electronic thermometers have reported that they are more accurate.[2][3] When a study compares measurements by different instruments as this one does, accuracy cannot be determined because we do not know the true value of the measured variable.[12] So, the focus of the study must be the agreement, that is, the relative consistency, of measurements by the different instruments.[13][14] Accordingly, the focus of this study was the relative consistency of temperature measurements by electronic and Galinstan thermometers. Reformulating the reports of greater accuracy of the two types of thermometers into that of greater consistency, the results of this study refute the reports of both the clinicians and the companies.

Variability of temperatures measured by two types of thermometers was assessed by correlations and standard deviations of raw measurements. Variability was also assessed by the standard deviations of mean differences between measurements by paired thermometers.

Correlations of Raw Scores

Table 2 shows the correlations between the temperatures measured by paired electronic and Galinstan thermometers. The correlation coefficient, r, (degrees of correlation) of the four paired temperatures ranged between 0.945 and 0.985. All four strong positive correlations were highly significant with p values of <0.0001. The mean r value was 0.972.

Standard Deviations of Raw Scores

According to Shanks et al.,[1,p.1263] the consistency of different measurements with two types of thermometers can be measured by the standard deviations of their different measurements. (The standard deviation can loosely be considered the average distance of measurements from the mean of all measurements with same thermometers.) In the four following subsections, analyses of standard deviations are used to interpret the results of the measurements taken in this study.

Reliability of Measurements by Electronic and Galinstan Thermometers. As noted above, some clinicians contend that electronic thermometers are less accurate than Galinstan thermometers,[7] and that electronic thermometers are less reliable than mercury and alcohol-in-glass thermometers.[24,p.17] Statistically, some results of this study are consistent with this view. However, the magnitude of the differences between measurements with electronic and Galinstan thermometers are of no practical clinical significance.

Three readings with electronic thermometers and one with Galinstan thermometers were outside two standard deviations from the mean. By the statistical-outlier criterion of consistency of measurements, then, Galinstan thermometers were more consistent.

Table 3 shows that the combined mean standard deviation of readings with the two electronic thermometers (E1 and E2) was wider than that of the two Galinstan thermometers (0.620 vs 0.536); the difference was only 0.084. The standard deviations of readings with individual thermometers show that one electronic thermometer (E1) and one Galinstan thermometer (G2) had the smallest spreads of readings. The other electronic (E2) and Galinstan (G1) thermometers had the widest spreads. If the aim in selecting thermometers, then, is less variability in readings, the electronic-1 and the Galinstan-2 thermometers would be preferable.

Mean Differences Between Readings with Electronic and Galinstan thermometers. Jensen et al.,[9] based on their study results, wrote that a standard deviation of temperature differences as low as 0.41°C (0.74°F) was unacceptable.[9] This unacceptable value is markedly larger than those in this study with both electronic and Galinstan thermometers. In this study, the mean difference for different pairs of thermometers ranged from 0.076 F (0.042 C) to 0.203 F (0.113 C), and the combined mean difference for all paired thermometers was 0.126 F (0.070 C).

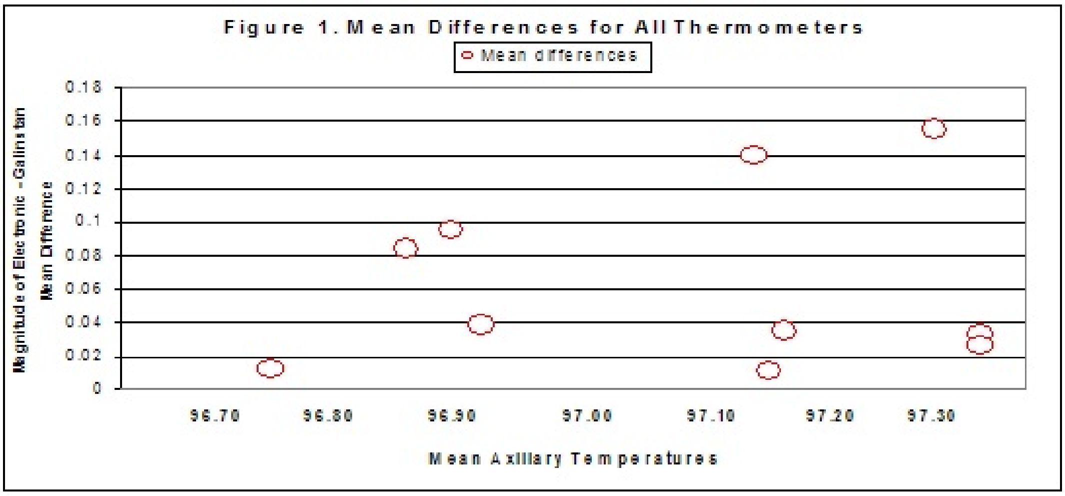
Figure 1. Mean Differences for All Thermometers

In this study, the mean standard deviation for the four sets of measurements with Galinstan thermometers was 0.52 F (0.29 C). This is slightly less than the mean standard deviations of measurements with two brands of electronic thermometers and a mercury thermometer reported by Shanks et al.,[1] which they considered acceptable. Measurements with the three instruments in their study had standard deviations of the order of only 0.54 F (0.30 C). This is the same value as the standard deviations of the measurements in this study with the Galinstan thermometers, 0.54 F (0.30 C), and less than the mean standard deviation of readings with the electronic thermometers, 0.62 F (0.34 C). These mean standard deviations, however, should *not* lead to the conclusion that electronic thermometers are less consistent than Galinstan themometers: as noted in the above section, one electronic and one Galinstan thermometer had a smaller spread of readings than did the other electronic and Galinstan thermometers.

Consistency of Measurements with Individual Thermometers of Each Type. The mean standard deviations of measurements with Galinstan thermometers, compared to those with electronic thermometers, give a false impression that the readings with Galinstan thermometers are markedly more consistent. A more definitive analysis, however, shows that this is not true.

The standard deviations in Table 1, Table 2, and Table 3 show that the mean standard deviation of the four sets of measurements with Galinstan thermometers was 0.517; the mean standard deviation of readings with electronic thermometers was 0.559. Obviously, the *mean* spread of readings with Galinstan thermometers around the mean measurement is less than that with electronic thermometers. However, this mean spread is a product of the grouping of the two Galinstan thermometers' readings.

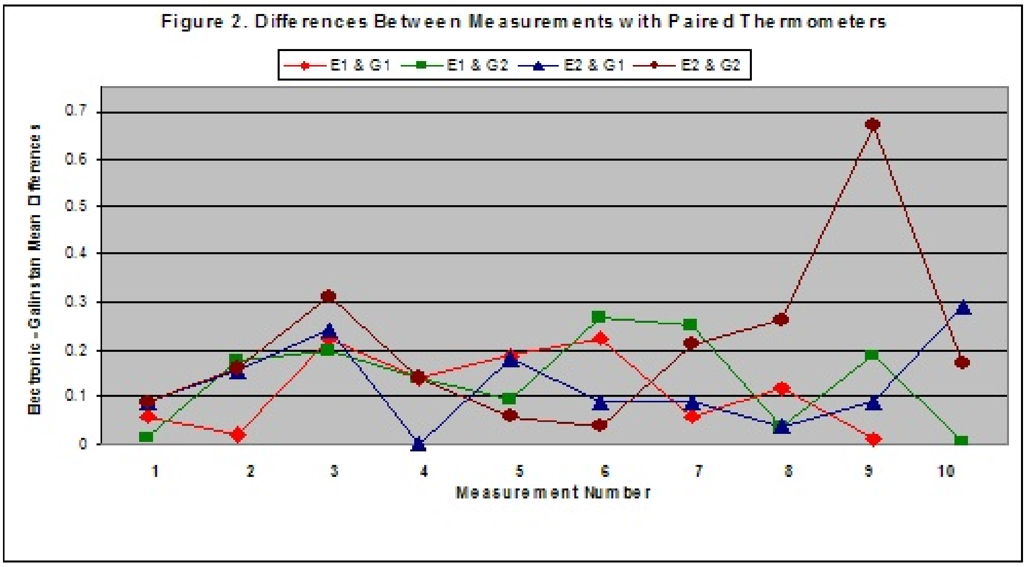
Figure 2. Differences Between Measurements with Paired Thermometers

Consider the standard deviations of readings for each type of thermometer shown in Table 3. The standard deviation of measurements with the electronic-1 thermometer was 0.510; that of the electronic-2 thermometer was 0.643. The standard deviation of measurements with the Galinstan-1 thermometer was 0.617, and that of the Galinstan-2 thermometer was 0.447. These standard deviations indicate that of the two electronic instruments, the electronic-1 thermometer was more consistent than the electronic-2 thermometer; and of the two Galinstan thermometers, the Galinstan-2 thermometer was more consistent. Of importance in considering whether Galinstan thermometers are more consistent than electronic thermometers is this: the spread of readings around the mean for the electronic-1 thermometer was less than that for the Galinstan-1. One electronic thermometer (E1) and one Galinstan thermometer (G2) had narrower spreads of readings than did the other electronic thermometer (E2) and the other Galinstan thermometer (G1).

There is no way to determine from the data in this study why measurements with one instrument were more or less consistent than those of another. For practical clinical purposes, the relative inconsistency of the readings with the different instruments may not be important. Measurements with all the thermometers were so close that, as Table 1 shows, the means of measurements with different thermometers did not significantly differ. Moreover, as Table

2 shows, because the measurements positively correlated so tightly, the probability that the correlations were due to happenstance is less than 1 in 10,000. Galinstan thermometers as a type of instrument, then, did not reliably give more consistent readings that did electronic thermometers.

Standard Deviations of Mean Differences Between Paired Thermometers. The differences between the mean axillary temperatures by pairs of electronic and Galinstan thermometers was less than the mean difference reported by Smith.[11,p.7] The mean differences in this study were well below the 0.36 F (0.2 C) criterion for including thermometers in human studies. Because of this, the electronic and Galinstan thermometers studied should be considered acceptable for both research and clinical use.

Limitations and Qualifications

The study was unblinded and therefore possibly involved observer bias. There was no vested interest in the outcome of the study. However, when a study is not randomized and at least some of the measurements are not digitalized, some terminal digits tend to be preferred (most often 0 and 5) and others not (1 and 9).[19] Such preferences may have contaminated the interpretation of some temperature readings of the Galinstan analog thermometers.

This study was *in vivo*, which means that variables extraneous to the thermometers used may account for much of the variation in temperature readings that are reflected in at least some of the statistical outcomes. The precision of measurements with the electronic and Galinstan thermometers would best be determined by *in vitro* testing, such as thermostatically-controlled water baths.[10,p.1550]

The small degrees of inconsistence in temperature readings with both types of thermometers may have been due to factors other than the technical precision of the devices. Collins and Exton-Smith noted that the readings of mercury thermometers usually do not significantly differ from the digital readouts of electronic instruments. Differences in readings typically result from how the thermometers are used.[10,p.1550] They noted that the patient may place the thermometer in a slightly different anatomical location on two different occasions, the thermometer may not be left in place long enough for it to equilibrate, or the ambient temperature may vary. A number of researchers have reported that rectal temperature readings are the most consistent with different types of thermometers.[9][11][15][18] Compared to the rectum, the less compact axilla may have differences in macro- and microcirculation, fatty layers, skin pockets, or adjacent muscle tissue, and these may cause variations in temperature readings even when a thermometer is carefully placed deep in the armpit. Such factors may account for much of the inconsistency in temperature measurements in this study.

The protocol of using more than one thermometer simultaneously was followed, as it was in other studies comparing different instruments.[1][11] In one study, subjects placed the tips of three thermometers under the tongue.[1,p.1263] The subjects positioned the thermometer tips as close to one another as possible. In another study, subjects used a Galinstan-in-glass thermometer beneath the tongue on one side of the mouth close to the sublingual artery; at the same time, a mercury thermometer was used on the contralateral side of the mouth.[11,p.3] Whether these procedures ensure maximally close temperature readings is not certain. In this study, it is possible that some closely adjacent anatomical sites in the subject's left axilla had enough difference in artery distribution that one thermometer accurately recorded a real temperature difference. Alterations in readings with different thermometers on different occasions may account for some of the variability in measurements that is reflected in some statistical outcomes of this study.

A criticism of axillary temperature measurement, expressed by Schmitz et al.,[15] is that it does not correlate well with the core temperature using the pulmonary artery temperature (determined by artery catheterization) as a point of reference. They found that rectal temperature correlated best, followed by the oral and ear cannel temperatures.[15] Lefrant et al.[18] reported that axillary temperatures differed from pulmonary artery temperatures (measured through pulmonary artery catheter) by 0.27 C (0.49 F). They studied critically ill patients in intensive care hospital units. In this patient population, obtaining temperatures as close to the core temperature (operationally defined as the pulmonary artery temperature) may be crucially important. But in the diagnosis and treatment of hypothyroid and peripheral thyroid hormone resistance patients, knowing the core temperature as closely as possible is not crucial. Instead, what is of importance is to quantify the mean basal temperatures during treatment and to compare these with the mean baseline basal temperature. The changes in temperature, then, are what is important rather than the relationship of the axillary temperature to the core temperature.

The value of using the axillary temperature in the diagnosis and treatment of hypothyroidism and peripheral thyroid hormone resistance is not diminished by its putative lower correlation with the core temperature. The rectum and the mouth are less preferable for different reasons. Most patients to whom rectal measurements have been recommended have declined to use the anatomical site. The oral temperature is reported to vary more than the axillary temperature because of intermittent subclinical inflammation of the nose, sinuses, or the mucosa of the mouth.[16,p.45] A recent study in Tel Aviv showed that oral mucositis raised the oral temperature but did not raise the systemic temperature.[17] It is possible that a high concentration of inhaled particulate matter in urban areas and allergens in rural areas may cause oral mucositis and a variably raised oral temperature.

Schmitz et al.[15] wrote that their study of thermometry underscored the importance of consistency in the method of measuring the temperature to establish temperature trends.[15] For this purpose, basal axillary temperatures, measured with either electronic or Galinstan thermometers, seem well suited.

Cost and Relative Merits of Electronic and Galinstan Thermometers

Galinstan thermometers (such as the Geratherm) and electronic thermometers are inexpensive, but the former usually costs less. Both types generally cost fewer than $15.00. Historically, mercury thermometers have been the least expensive, Geratherm thermometers have been midrange, and electronic thermometers have been the highest- priced.[6,p.25]

Advantages of electronic thermometers over Galinstan thermometers are that less time is needed to record temperatures (this is called "temporal convenience [10,p.1550]), and they are designed to beep when the peak temperature is reached.[6,p.25] A disadvantage of these instruments is that the power contained in their button batteries is eventually expended. An advantage of the Geratherm Galinstan-containing "hypothyroid thermometer is that, between its degree marks, it contains marks for 10ths of a degree that are highly visible. The Galinstan thermometer, then, allows for finer graduations of temperature measurement than is povided by electronic thermometers.

Conclusion

In this comparative study, temperature measurements with electronic and Galinstan thermometers were consistent enough to be of reliable clinical use. A corollary finding is that the use of the same axilla of one subject provided the consistent temperature readings. This indicates that careful placement of either type of thermometer deep in the same armpit is a reliable clinical procedure for patients.

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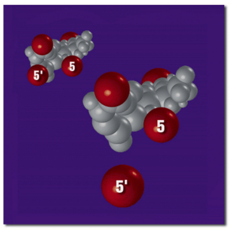
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Prevalence of Thyroid Dysfunction and Its Effect on Serum Lipid Profiles in a Murzok, Libya Population

(Full Text Free in pdf format)

Ali M. Nouh, Ibrahim A. M. Eshnaf, and Mohamed A. Basher

Sebha University Faculty of Engineering and Technology
Department of Medical Laboratory Sciences

Contact: Ali M. Nouh alinouh12@yahoo.com

ABSTRACT. The objective of this study was to assess the prevalence of thyroid dysfunction and its correlation with serum hyperlipidemia among the adult population of Murzok City, Libya. Blood samples were collected randomly from 356 subjects (179 male and 177 female) in the age range of 20-to-65 years. The blood was analyzed for the levels of total T3, total T4, free T4 and TSH by electrochemiluminescence immunoassay (ECLIA). Lipid levels of total cholesterol, triacylglycerol (TAG), LDL, and HDL were measured using the enzymatic colorimetric method.

The prevalence of thyroid dysfunction types was the following: overt hyperthyroidism (0.84%), subclinical hyperthyroidism (0.84%), overt hypothyroidism (1.12%), and subclinical hypothyroidism (6.18%). Also, thyroid dysfunction was more common in females (0.56%, 0.84%, 0.84%, and 4.21%) than in males (0.28%, 0.00%, 0.28%, and 1.97%).We found a higher prevalence of subclinical hypothyroidism (27%) among the subjects with hypercholesterolemia. We also found a significant negative correlation between subjects with normal T3 and hypercholesterolemia ($P<0.05$), and a significant positive correlation between subjects with 4 high T and HDL ($P<0.05$).

Keywords. Hypercholesterolemia • Libya • T3 • T4 • Thyroid dysfunction prevalence • Triacylglycerol • TSH

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Sebha University Faculty of Engineering and Technology
Department of Medical Laboratory Sciences

Contact: Ali M. Nouh alinouh12@yahoo.com

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Abstract. The objective of this study was to assess the prevalence of thyroid dysfunction and its correlation with serum hyperlipidemia among the adult population of Murzok City, Libya. Blood samples were collected randomly from 356 subjects (179 male and 177 female) in the age range of 20-to-65 years. The blood was analyzed for the levels of TT_3, TT_4, FT_4, and TSH by electrochemiluminescence immunoassay (ECLIA). Lipid levels of total cholesterol, triacylglycerol (TAG), LDL, and HDL were measured using the enzymatic colorimetric method.

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Keywords. Hypercholesterolemia • Libya • T_3 • T_4 • Thyroid dysfunction prevalence • Triacylglycerol • TSH

Introduction

Historically, methods for classifying patients with milder degrees of thyroid dysfunction have undergone dramatic changes. Classification has involved clinical, biochemical, and immunologic criteria.[1][2] The serum TSH assay is an accurate test for detecting out-of-range circulating levels of thyroid hormone. Subclinical hypothyroidism is defined as an elevated TSH level with reference range thyroid hormone levels. This disorder is found in 6%-to-8% of adult women and 3% of adult men.[6] It can be associated with reversible hypercholesterolemia.[6][7][8]

Women have a higher incidence of overt hyperthyroidism (a TSH level less than 0.1 mU/L with high levels of thyroid hormones[9]), and the incidence increases with advancing age.[6][10][11][12][13][14] Subclinical hyperthyroidism (a TSH level less than 0.1 mU/L with normal thyroid hormone levels[15]) has been associated with a higher incidence of atrial fibrillation in older persons.[11]

The prevalence of thyroid dysfunction is defined by testing patients in geographic areas, primary care clinics, and in populations that have not been screened previously.[16][17] Thyroid function tests are recommended in populations with high health risks, including lipid disorders, goiter, autoimmune disorders, infertility, women after menopause, and women who are pregnant or postpartum.[18]

Materials and Methods

Blood samples were obtained from 356 subjects, 179 male and 177 female. Age of the subjects ranged from 20-to-65 years. Our sample of 356 subjects was 10% of the population of Murzok City in this age range. Venous blood samples were drawn after 8-to-12 hours of overnight fasting. Blood samples were left to clot and serum samples were separated and kept in two plain tubes. The tubes were labeled as Total T_3 (TT_3), Total T_4 (TT_4), Free T_4 (FT_4), and TSH. The tubes were stored and later assayed using a Roche Elecsys 2010 analyzer and reagents.

The lipid profile included the total cholesterol, triacylglycerol (TAG), LDL, and HDL. These were measured by the COBAS INTEGRA autoanalyser system using the corresponding Roche diagnostic kits. The Minitab Graph Statistical Analysis program

Table 1. Thyroid dysfunction in all subjects and sex.

Diagnosis	**Total**	**Male**		**Female**		**Total**
	%	Number	%	Number	%	Number
Normal		170		154		324
Overt hyperthyroidism	0.84	1	0.28	2	0.56	3
Subclinical hyperthyroidism	0.84	0	0.00	3	0.84	3
Overt hypothyroidism	1.12	1	0.28	3	0.84	4
Subclinical hypothyroidism	6.18	7	1.97	15	4.21	22
Total		179		177		356

Table 2. Mean values of T_3, T_4, f T_4 and TSH in thyroid dysfunction subjects.

Dysfunction	**No.**	**T_3**	**T_4**	**Free T_4**	**TSH**
		Mean(SD) nmol/L	Mean(SD) nmol/L	Mean(SD) pmol/L	Mean(SD) µU/L
Overt hyperthyroidism	3	4.4±1.5	199±32	30.2±8.8	0.01±0.00
Subclinical hyperthyroidism	3	2.1±0.5	119±19	17.1±4	0.01±0.00
Overt hypothyroidism	4	1.6±0.2	82±11	10.6±1.3	20.6±12
Subclinical hypothyroidism	22	2.1±0.5	109±25	13.6±2.4	3.3±1.3
Total	32				

Table 3. Mean values of T_3, T_4, FT_4 and TSH in normal and abnormal subjects.

Variables	**Number Mean (SD)**	
	Normal	**Abnormal**
T_3 (nmol/L)	346 ^{a}2.1±0.41	10↑ ^{b}3.7±0.41
T_4 (nmol/L)	351 ^{a}111±22	5↑ ^{b}217±26
FT_4 (pmol/L)	324 ^{a}15±1.7	3↑ ^{b}30±9
FT_4 (pmol/L)	324 ^{a}15±1.7	29↓ ^{b}11±0.95
TSH (µU/L)	337 ^{a}1.7±0.98	13↑ ^{b}5.5±2.1
TSH (µU/L)	337 ^{a}1.7±0.98	6↓ ^{b}0.006±0.001

$^{a, b}$ *Mean values with different superscripts are significantly different (P<0.01).*

was used for statistical analyses of our results.

Results

We diagnosed thyroid dysfunction by the use of thyroid function tests.[6][3][15][18] These included TT_3, TT_4, FT_4, and the TSH. The reference range for the TT_3 was 1.3-to-3.1 nmol/L, for the TT_4 was 66-to-181 nmol/L, for the FT_4 was 12-to-22 pmol/L, and for the TSH was 0.3-to-4.2 µU/L). The manufacturers of the assay kits recommended these ranges.

Tables 1 and 2 show the results of the diagnoses. We found that three subjects (0.84%), one male (0.28%) and two females (0.56%), had a low mean TSH value (0.01±0.0 µU/L). They also had high mean thyroid hormone levels, T_3, T_4 , FT_4 (4.4±1.5 nmol/L, 199±32 nmol/L, 30.2±8.8 pmol/L, respectively). We diagnosed these subjects as having overt hyperthyroidism. The 0.84% prevalence of overt hyperthyroidism in our study is lower than the 1.9% prevalence among Brazilians.[21] However, it is higher than the 0.3% among Japanese subjects,[19] 0.5% in Koreans,[20] 0.5% among Englanders,[22] and 0.5% among Americans.[26]

We diagnosed three female subjects (0.84%) as having subclinical hyperthyroidism. They had a low mean TSH value (0.01±0.0 µU/L) and reference range mean values for T_3, T_4 , FT_4 (2.1±0.5 nmol/L, 119±19 nmol/L, and 17.1±4 pmol/L, respectively). This prevalence among our subjects of 0.84% is in agreement with previous studies.[24][25] Those studies showed a lower incidence of subclinical hyperthyroidism among middle-age subjects and a higher incidence among subjects more than 60 years old.

Four subjects (1.12%), one male (0.28%) and three females (0.84%), were diagnosed as having overt hypothyroidism.[4][5] They had a high mean TSH value (20.6±12 µIU/L) and a low mean reference range value for T_3 and T_4 (1.6±0.2 nmol/L, 82±11 nmol/L, respectively). Their mean FT_4 level was low (10.6±1.3 pmol/L). The 1.12% prevalence of overt hypothyroidism among our subjects does not differ from that reported among the Japanese (1.1%)[19] and Brazilians (1.4%).[21]

Twenty-two subjects (6.18%), seven males (1.97%) and fifteen females (4.21%), were diagnosed as having subclinical hypothyroidism. They had a high mean reference range TSH value (3.3±1.3 µU/L) and mean reference range values for the T_3, T_4, and FT_4 (2.1±0.5 nmol/L, 109±25 nmol/L, 13.6±2.4 pmol/L, respectively). The 6.18% prevalence of subclinical hypothyroidism among our subjects is higher than that reported among Americans (4.3%)[26] and Brazilians (5%).[27] However, our prevalence is lower than that reported among Japanese (8.7%)[19] and Englanders (8%).[22]

For thyroid variables, our study shows a highly significant difference ($P<0.01$) between subjects' TSH and abnormal thyroid hormone levels. This is true for levels that are above or below the reference ranges (see Table 3).

In this study, the prevalence of thyroid dysfunction was more common among women than men (Table 1). The percentage of thyroid dysfunction among women was 13% and among men was 5%. The difference in the prevalence may result from immunological changes that increase or decrease thyroid hormone levels during pregnancy and the postpartum period. These prevalence differences between subjects in this study and others may be due to differences in age, gender, family history, and pathophysiologic conditions. Results of this study, however, are within the prevalence limits established by other studies.

Table 3 shows the results of mean values of T_3, T_4, FT_4, and TSH among subjects with different thyroid diagnoses. The difference between the mean values for thyroid hormone parameters that are within and outside the reference ranges is significant ($P<0.01$).

These results show that 346 subjects were found to have normal levels of T_3 (2.1±0.41 nmol/L) and 10 subjects had high levels of T_3 (3.7±0.41 nmol/L); whereas 351 subjects had normal levels of T_4 (111± 22 nmol/L) and five subjects had high T_4 levels (217 ±26 nmol/L). In this study, 324 subjects had normal FT_4 levels (15±1.7 pmol/L), 3 subjects had high FT_4 levels (30±9 pmol/L), and 29 subjects had low FT_4 levels (11±0.95 pmol/L).

With regard to TSH measures, 337 subjects had normal TSH levels (1.7±0.98 µU/L). Thirteen subjects had high TSH levels (5.5±2.1 µU/L), and 6 subjects had low TSH levels (0.006±0.001 µU/L).

Mean values of the various parameters of lipid profile in all subjects are shown in Table 4. The difference between means of normal (N) and abnormal (Ab) subjects is significant ($P<0.05$). The mean value of normal total cholesterol (TC) for 278 subjects was 155±27 mg/dl. The mean value of TC for 78 subjects was abnormal at 229±26 mg/dl. The mean value of TAG was normal for 261 subjects (117±42

Table 4. Mean values of TC, TAG, and LDL in normal and abnormal subjects.

Variables	**Number Mean (SD)**	
	Normal (N)	**Abnormal (Ab)**
TC (mg/dL)	278 ^{a}155±27	78 ^{b}229±26
TAG (mg/dL)	261 ^{a}117±42	95 ^{b}285±70
LDL (mg/dL)	256 ^{a}93±22	100 ^{b}153±21

^{a,b}*Mean values with different superscripts are significantly different ($P<0.05$).*

Table 5. Correlation of thyroid parameters and lipid profiles in all subjects.

Variables		**TC**	**TAG**	**HDL**	**LDL**
		r^2	**r^2**	**r^2**	**r^2**
T_3	N	-0.114*	-0.020	-0.021	-0.106*
	H	-0.046	-0.097	-0.434	0.021
T_4	N	-0.029	-0.066	0.095	-0.012
	H	0.807	-0.019	0.951*	-0.541
FT_4	L	-0.470*	-0.478**	0.269	-0.438*
	N	-0.073	-0.196*	0.215**	-0.063
	H	-1.000*	0.570	-0.031	-0.944
TSH	L	0.403	-0.449	0.162	0.066
	N	0.104	0.073	-0.117*	0.122*
	H	0.652*	0.213	0.050	0.609

***Correlation is significant at <0.01 level (2-tailed).*
**Correlation is significant at ≤0.05 level (2-tailed).*
N=Normal, H=High, L=Low.
r^2=coefficients of correlation.

mg/dl) and abnormal for 95 subjects (285±70 mg/dl). In addition, 256 subjects had normal LDL (mean value was 93±22 mg/dl), and 100 subjects had abnormal LDL (mean value was 153±21 mg/dl).

As shown in Figure 1, 78 subjects had high cholesterol levels (22%), 95 subjects had high triacylglycerol (27%), and 100 subjects had low density lipoproteins (28%). In addition, Figure 2 shows that 21 subjects (7 males and 14 females) had subclinical hypothyroidism among all subjects with high cholesterol levels. These 21 subjects are 27% of the total number of subjects (78) with high cholesterol. This percentage is higher than that in a study reported in Italy (10%),[28] and we also show an increase in numbers of females over males.

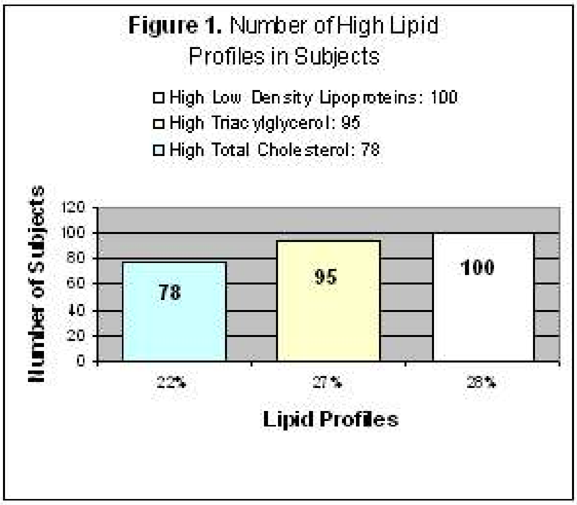

Figure 1. Number of High Lipid Profiles in Subjects

The coefficients of correlation between the thyroid values and the lipid values are shown in Table 5. There was a significant negative correlation between T_3 (normal) and each of TC and LDL parameter values ($P<0.05$). A positive correlation was significant between T_4 (high) and HDL ($P<0.05$).

Negative correlations were also found between FT_4 (low) and each of TC ($P<0.05$), TAG ($P<0.01$), and LDL ($P<0.05$). FT_4 (normal) had a significant negative correlation with TAG ($P<0.05$), and a positive correlation with HDL ($P<0.01$). There was a significant negative correlation between FT_4 (high) and TC ($P<0.05$).

Normal TSH negatively correlated with HDL and positively correlated with LDL significantly ($P< 0.05$). A significant positive correlation was found between TSH (high) and TC ($P<0.05$).

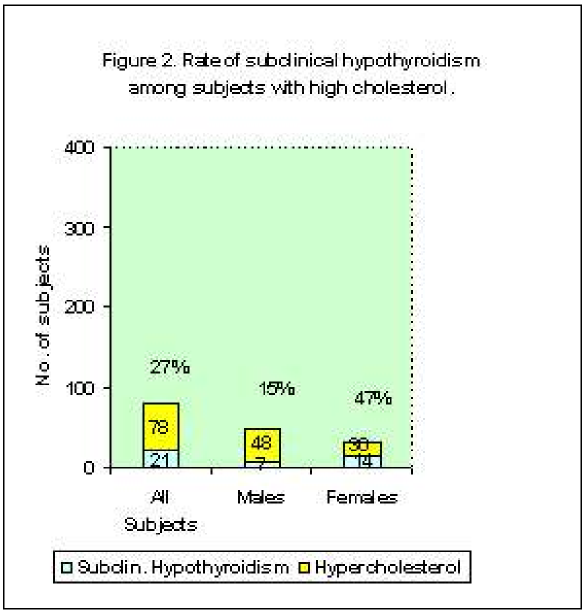

Figure 2. Rate of subclinical hypothyroidism among subjects with high cholesterol.

Conclusion

In the Murzok City, Libya population we studied, thyroid dysfunction was more common among females than males. Our results showing an association between thyroid dysfunction and hyperlipidemia agree with the results of previous studies.[23][26][29][30] In addition, among subjects with hypercholesterolemia, subclinical hypothyroidism was more common.

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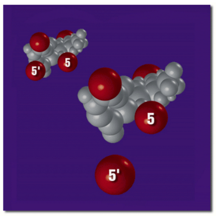

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Metabolic Failure as the Cause of Fibromyalgia Syndrome: Exploring the John C. Lowe Thesis

(Full Text Free in pdf format)

Bjørn Johan Øverbye, MD*

*Postbox 348 –N4803, Arendal, Norway, Contact: bjorn@dr-overbye.no

Abstract. Introduction and Aim. The aim of this one year project was to investigate a thesis by John C. Lowe: that fibromyalgia syndrome (FMS) is a hypometabolic condition caused by a reduced effect of thyroid hormones at the cellular level, due either to (1) a deficiency of adequate thyroid hormone (hypothyroidism), or (2) a reduced cellular effect of thyroid hormone despite its production of reference range quantities (partial peripheral thyroid hormone resistance).

Material and Methods. Study subjects were 56 female patients with a clinical picture of "classical FMS." The diagnosis of FMS was verified by specialists for 27 of the patients. Although 29 patients had the classical signs and symptoms of FMS, they were waiting for their diagnosis to be verified by specialists. These 29 patients were excluded from the investigation until a later date when a qualified specialist will verify beyond doubt their correct diagnostic label.

To test Lowe’s thesis, a questionnaire was made. The basis of the questionnaire was the already-existing statistics of symptoms and signs of hypothyroid patients who had not yet achieved metabolic restoration by the use of thyroid hormone medication. The questionnaire was filled out by all 56 patients. The answers from all patients were collected and put into a database. The answers of patients with verified FMS were extracted and compared to the statistical material upon which the questionnaire was made.

In addition, all 27 patients with verified FMS were tested for their thyroid hormone status at the local hospital. Thirteen of the patients were tested with a method developed by Professor Louis-Claude Van Vincent,[45] "Van Vincent’s Bio-Electrical-Terrain-Analysis" (Van Vincent BE-T-A). BE-T-A is a system that evaluates the metabolic status of mesenchymal (structurally supportive) and parenchyma (essentially producing) tissues.[16]

Results. Comparing the questionnaire answers of the 27 FMS patients with the statistics from hypothyroid patients, the frequencies of symptoms fit a pattern of untreated hypothyroidism. The Van Vincent BE-T-A test showed an acidosis of mesenchymal tissues, such as connective tissues and lymphatic and blood vessels. The acidosis can be explained by a lack of thyroid hormone effect at the cellular level, leading to an increase in parenchymal anaerobic metabolism, in which biological processes proceed in the absence of oxygen.

Conclusion. The results of questionnaire analysis, use of the Van Vincent BE-T-A testing, and the author's clinical experience are consistent with the Lowe thesis that metabolic failure underlies FMS. The cause of the failure is plausibly explained by deficiencies of thyroid hormones or reduced cellular effects of the hormones. There are two natural solutions to this problem: (1) increase the amount of thyroid hormones available to the tissues, and (2) normalize the cellular effects of thyroid hormones by removing whatever hinders their normal effects.

KEYWORDS: Fibromyalgia syndrome, hypothyroidism, thyroid hormone resistance, Van Vincent BE-T-A test, Bio-Electrical–Terrain-Analysis, energy medicine, John C. Lowe Thesis

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Metabolic Failure as the Cause of Fibromyalgia Syndrome: Exploring the John C. Lowe Thesis

Bjørn Johan Øverbye, MD*

*Postbox 348 –N4803, Arendal, Norway, *Contact:* bjorn@dr-overbye.no

ABSTRACT. ***Introduction and Aim.*** The aim of this one year project was to investigate a thesis by John C. Lowe: that fibromyalgia syndrome (FMS) is a hypometabolic condition caused by a reduced effect of thyroid hormones at the cellular level, due either to (1) a deficiency of adequate thyroid hormone (hypothyroidism), or (2) a reduced cellular effect of thyroid hormone despite its production of reference range quantities (partial peripheral thyroid hormone resistance).

Material and Methods. 56 female patients with a clinical picture of "classical FMS." The diagnosis of FMS was verified by specialists for 27 of the patients. Although 29 patients had the classical signs and symptoms of FMS, they were waiting for their diagnosis to be verified by specialists. These 29 patients were excluded from the investigation until a later date when a qualified specialist will verify beyond doubt their correct diagnostic label.

To test Lowe's thesis, a questionnaire was made. The basis of the questionnaire was the already-existing statistics of symptoms and signs of hypothyroid patients who had not yet achieved metabolic restoration by the use of thyroid hormone medication. The questionnaire was filled out by all 56 patients. The answers from all patients were collected and put into a database. The answers of patients with verified FMS were extracted and compared to the statistical material upon which the questionnaire was made.

In addition, all 27 patients with verified FMS were tested for their thyroid hormone status at the local hospital. Thirteen of the patients were tested with a method developed by Professor Louis-Claude Van Vincent,[45] "Van Vincent's Bio-Electrical-Terrain-Analysis" (Van Vincent BE-T-A). BE-T-A is a system that evaluates the metabolic status of mesenchymal (structurally supportive) and parenchyma (essentially producing) tissues.[16]

Results. Comparing the questionnaire answers of the 27 FMS patients with the statistics from hypothyroid patients, the frequencies of symptoms fit a pattern of untreated hypothyroidism. The Van Vincent BE-T-A test showed an acidosis of mesenchymal tissues, such as connective tissues and lymphatic and blood vessels. The acidosis can be explained by a lack of thyroid hormone effect at the cellular level, leading to an increase in parenchymal anaerobic metabolism, in which biological processes proceed in the absence of oxygen.

Conclusion. The results of questionnaire analysis, use of the Van Vincent BE-T-A testing, and the author's clinical experience are consistent with the Lowe thesis that metabolic failure underlies FMS. The cause of the failure is plausibly explained by deficiencies of thyroid hormones or reduced cellular effects of the hormones. There are two natural solutions to this problem: (1) increase the amount of thyroid hormones available to the tissues, and (2) normalize the cellular effects of thyroid hormones by removing whatever hinders their normal effects.

KEYWORDS: Fibromyalgia syndrome, hypothyroidism, thyroid hormone resistance, Van Vincent BE-T-A test, Bio-Electrical–Terrain-Analysis, energy medicine, John C. Lowe Thesis

INTRODUCTION AND AIM

"The problem is not lack of knowledge, but knowing what we already know" ● Norwegian author Wilhelm Schjeldrup MD

PART I: A MEDICAL PROBLEM, BUT NO SOLUTION

Medical Science in Need of New Concepts. Medical science has a long standing history for sacrificing complexity to simplicity by using the tradition of "diagnosing"—giving one single noun to disease-entities that often covers a wide range of symptoms and signs; often going to extreme dichotomy by neglecting the fact that a body is one whole: body, mind, and soul. As observed by O'Connor: "Medical diagnoses are nominalizations. They are substantives, but every disease is a process, and changes during the process of therapy."[1] Such simplemindedness, which omits a host of information, can be justified for simple cases like a broken leg, a torn tendon, or a cut in the skin; where just a single noun is sufficient to transmit inherent meaning; but dealing with complex diseases, single nouns pointing to simple entities fail their purpose dramatically.

Fibromyalgia, the topic of this paper, is not a "simple, fixed entity." It cannot be clearly identified by a set of criteria; experience with in depth study of patients given the diagnosis shows a broad spectrum of symptoms, signs, and objective findings.[2] The spectrum is indeed so broad that the noun "syndrome" is proper, denoting a variety of symptoms, signs, and objective findings that can vary in number and intensity over a spectrum of possibilities.[3]

Recording the finer details leads to even deeper realizations that fibromyalgia syndrome, due to its flexible nature, ought not be regarded as a simple entity. Instead, it should be considered a condition more on the order of "functional diseases." Such diseases is a new concept formed in the latter part of the 20th century when cybernetics and the idea of function entered medicine from the science of physics and biology. Using system thinking and cybernetics, FMS is best seen as a system failure to achieve maximum functionality and energy production, resulting in a host of energy-depletion signs, symptoms, and findings.[4]

However, in the history of medicine, doctors have a long tradition of lagging behind current advances in thinking and technology. They have, despite "modern times," kept searching for simpler "one-noun, one-entity concept" that adheres to the unspoken diagnostic tradition. This thereby pleasing their peers who, for some reason, have built empires upon simple and manageable doctrines that in due time have become the credo of the profession as to what or what not to believe.[5]

However, from time-to-time comes great minds to shake up the public, and the recent works of a number of American researchers have brought to light the fact that what is considered disease entities are but fleeting changes in the human framework, as energy is reduced in a number of steps to save life from harmful influences: destruction by environmental toxins,[6] lack of proper nutrients,[7] psychological and social stress,[8] electromagnetic pollution,[9] and the misuse of potent modern drugs that have serious side effects meant to be used only for a short time span.[10] Due to such influences, we see a decline in the human adaptation system and immunological defense, which in turn lays the body open to all sorts of microbes (natural or man made).[11]

John C. Lowe Discovery: FMS—Just Like Hypothyroidism. One of these giants among minds is current researcher and science writer John C. Lowe who has delivered a major blow to the concept of one name, one diagnosis, one pathology. His book *The Metabolic Treatment of Fibromyalgia*[12] will stand as one of the major intellectual efforts of this century to speak out for a functional interpretation of human suffering. According to the book, FMS and also chronic fatigue syndrome (CFS) are not fixed entities easily contained in the meaning of the one-noun tradition. Instead, they are complex phenomena resulting from lack of energy produced per-unit body mass to sustain proper functions and life under the ruling conditions of life.[12,pp.295-341] Thereby, he has taken away FMS and CFS from the backwaters of nominalization to where real life is, and described the process to which the diagnostic noun points.

Looking to the underlying processes and the resulting clinical scenarios, rather than to the semantics, Lowe has discovered that FMS and CFS patients have exact, if not identical, manifestations of symptoms as people deficient in thyroid hormone, whom we say have "hypothyroidism."[12,pp295-341]

The exception is that in the two former "diseases," FMS and CFS, traditional testing does not show a deficiency of thyroid hormones. Therefore, patients appear to be "euthyreots." That is, they appear to have "have sufficient thyroid function compared to a sample of normally functioning human beings." But facts speak for themselves: these patients have most if not all the symptoms and signs of people diagnosed as being hypothyroid.[12,pp1107-1127]

In addition, Lowe has recently found in two well-controlled studies, using indirect calorimetry, that FMS patients—some of whom were euthyreots—had significantly lower resting metabolic rates and basal body temperatures than matched healthy controls.[86][87]

According to Lowe, it is therefore intellectually proper to term these two groups of patients, and especially fibromyalgia patients (about which most of the book is written), as hypometabolic, despite being "euthyreot."[12,pp243-288] Logically, the patients' cells must be somehow resistant to the influence of hormones from the thyroid gland.[17] This concept is new to most doctors, but there is no way around the situation: If your laboratory tests spell "hormones within their ranges," but the clinical picture tells you that the effect of the hormones are lacking, what other choice is there but to call the patient's condition "hormonal resistance" or "reduced effects of thyroid hormones"?[18]

MATERIALS AND METHODS

"To find gold you either need a good map
or Grace of the gods." ● Norse saying

PART II: MAPPING ENERGY: DEPLETED TERRAIN

The Van Vincent Test: Mapping Hypometabolic Terrain. My own experience with Van Vincent testing dates some years back. As in this study, I have performed Van Vincent testing, taking measurements with equipment customarily used with our cancer patients, from the German company MedTronik.

Through this testing, I discovered that many patients with "unclear clinical pictures" and who were doomed to suffer from "inexplicable diseases," or described as "psychosomatic cases," were instead suffering from too little energy.

At that time, within the ordinary health care system in Norway, there was little-to-no lab service available to substantiate a diagnose of too little energy. So I had to rely on clinical evaluations and act accordingly, often with very good results.[15] But realizing that in the long run, the situation was unbearable, we finally invested in BE-T-A equipment. "BE-T-A" is an abbreviation for Bio-Electronic-Terrain-Analyzer.

The BE-T-A methodology makes it possible to quantify cellular metabolism by making a statistical analysis of bio-physical parameters of venous blood, sputum, and urine.[16]

I will explain the methodology: The BE-T-A method is a typical "Old world" bio-medical device rooted in the marriage of medicine, technology, and holistic thinking that emerged in Europe in the fruitful years from 1920-to-1960. The technique and methodology was single-handedly developed in Strasbourg in 1946 by French hydrologist Professor Louis-Claude Van Vincent. He originally designed the instrument to evaluate the quality of drinking water.[17]

Van Vincent could give a good picture of the quality of water by using three well-known physical measurements: pH (acidity), rH_2 (electron activity), and R (resistance).

During 1952 and 1953, while working in Lebanon, he began using his technique on human fluids: saliva, urine, and venous blood. As Elmau wrote, he "was able to show on a large patient base that the physical or bio-electronic measurement values pH, rH_2, and R—depending on how they relate to each other—are sufficient to indicate whether the organism is sick or healthy."[17,piii]]

As a result of his pioneering work, Van Vincent was appointed Professor at Ecole d`Anthropolgie in Paris. There he continued to build his database and refine his technical equipment. In the 1960ies, his method was introduced to the German-speaking world by Dr. Med. Franz Morell.

Later on, Van Vincent's method spread to all parts of the world. The first world congress on his method was held in Königstein in 1976. The proceedings of the International Society of Bioelectronic Van Vincent have since been applied to veterinary and human medicine, oncology, the evaluation of drinking water, agriculture, hygiene, and the dairy industry.[17,p.iv]

To understand the value of the Van Vincent methodology, one must understand the three basic components, pH, rH_2, and R, as indicators of cellular energy production. I explain each of these below.

pH: The Magnetic Factor. pH is basically a measurement for proton activity. In chemistry, substances that can give away protons are acids, and those that steal protons are alkalies. This leads to the standard textbook wisdom we learnt "back in School," give which goes back to the Danish chemist Bønsted, who in 1923 defined the terms:

(1) Acid-H → Alkali + H+

(2) Proton–donator (Acid) → Proton- acceptor (Alkali) + H+

When this reactions takes place in water it may look somewhat like:

(3) Proton-donator + H_2O → Proton-acceptor + H_3O+

pH is equal to the negative decadic logarithm of the concentration of protons in a given fluid. This turns out to be a measurement of proton activity in that fluid. The formula holds good for the range 4.0 to 9.2. For purified water at 18° Celsius, pH = 7.105. At 24° Celsius, pH = 7.0, and at 37° Celsius, pH = 6.78. This latter pH, 6.78, is optimum for kidney activity.

The difference in pH = 1 equals a factor of 10 in proton activity. At pH = 6.8, there is 160 nanomols of dissociated protons per liter of fluid. At pH = 7.4, there is only 40 nanomols of dissociated protons per liter. At theoretical pH = 0, there is a maximum proton activity (dissociated protons), and at pH = 14 there is no proton activity at all.

The technical side to the problem is taken care of with a glass-electron chain using two separate metal electrodes separated by a proper material. The electrode must be calibrated once a week and cleaned properly. If properly taken care in this way, it will have an accuracy of 0.02-to-0.04.

Measuring urine pH using dry chemistry, as with "Lab-stix," is often cherished in clinical practice. However, an interesting discovery is that, in comparison with dry chemistry, using electrodes to measure urine pH is highly accurate. (The dry chemistry, as with "Lab-stix," is often cherished in clinical practice. However, an interesting discovery is that using electrodes to measure urine pH is highly accurate.) By comparison, the dry chemistry method is highly inaccurate, giving low readings.[18]

Protons work like micro-magnets. Because of this, in a very proton-rich milieu (that is, a low pH or acidic milieu), there will be a stronger magnetic field than in an alkaline milieu.[25] pH thus is also an indirect measurement of a fluid's magnetic properties.

Even these considerations may be too simple for one to get the "whole picture." For example, according to Davis and Day, pure water is a mixture of 18 different molecular forms and 15 kinds of ions. These give rise to 36 different types of substances which may be in a mixture that, for simple reasons, we agree to call "water."[16,pp67-70]

rH_2: The Electron Activity Factor. The other entity in BE-T-A technology is rH_2. This is a measurement of the amount of negative electricity that is uniquely bound to the electron (e-). According to the Clark equation, rH_2 is defined as:[27]

(4) Definition: $rH_2 = -\log(PH_2)$

P stands for partial pressure exhibited by any gas. PH_2 stands for the partial pressure of hydrogen gas. Hydrogen gas arises due to the fact that water H_2O gives rise to both H^+ ions and OH- ions. If electrons are supplied to the water they will bind to protons: H^+ and from atomic hydrogen, H. The atom of hydrogen will bind to another hydrogen atom formed in the same manner, creating hydrogen gas. The amount of gas can be measured by a proper probe immersed in the fluid. With a calibrated meter, we can then read rH_2 on a scale.

In water, there is a balance between H_2 and O_2. The balance occurs because the surplus of OH- freed when H^+ goes to hydrogen gas forms oxygen (O_2). In water rH_2 will vary between 0 and go to +42. The neutral point of rH_2 is 28, where $PH_2 = PO_2$.

Below the neutral point of rH_2 (< 28) there is a surplus of electrons. Water becomes electronegative, and the partial pressure of oxygen is less than that of hydrogen. Above the neutral point of rH_2 (> 28), the situation is reversed.

For venous blood, the neutral point is defined differently, as the mean for healthy persons is $rH_2 = 22$. Compared to water, then, venous blood is in a slightly reducing state.[20,pp.25-30]

rH_2 is thus a measurements of the amount of negative electricity (electrons), while the more wide known pH is a measurement for positive electricity (protons). Both processes are of equal importance because they are dependent on each other; this applies to rH_2 as much as to pH. Generally this is not taken into consideration because most doctors do not have access to the "hidden" factor rH_2. But one should never forget: when there is an exchange of protons (pH), there is a simultaneous exchange of electrons (Rh_2).

Similar to the acid-alkali concept of pH, rH_2 leads to the concept of reduction-oxidation:

(5) Electron-donator → Electron-acceptor + e-

According to Nygren-Wigren in 1964:[20,pp.25-30]

(6) Oxidation: the oxidating substance donates an electron

(7) Reduction: The reducing substance accepts an electron

In shorthand, this is often written:

(8) Red → Ox + N → e-

(N represents the number of electrons transferred.) When the reaction goes to the right Y, we name it "Oxidation"; when it goes to left Z, we call it "Reduction."

The equation says that in any liquid where reduction and oxidation takes place, there is a "Red-Ox" pair. But to what use is this? As will later be shown, energy in the human body is of an electro-chemical nature; shifting around electrons in a number of Red-Ox processes generates free energy; that energy can be stored in energy-rich molecules, such as ATP and NADH. *The shift of electrons and their transport on ions is what in physics is called an "electrical current* (I)."

We are now entering useful territory: If you have pH, you can go to your textbooks and deduct useful information about the production and transport of acids. This is useful if you remember that anaerobic metabolism creates lactic acid, acidifying the internal milieu. Furthermore, if you know your Red-Ox potential, you know at least two things: the flow of electrical currents in body fluids and, if you know rH_2, you will have a fair estimate of free radicals, since free radicals are electron-grabbers and thus lower rH_2.

pH and rH_2 are interrelated, as will be seen form the so-called "Nernst Red-Ox potential equation":[20,p.94-96]

(9) Definition: $E = 30 \rightarrow (rH_2 - 2 \rightarrow pH)$

"E" *has to be calculated* on the basis of measurements of parameters rH_2 and pH. The unit used to measure E is volt (V). In biological samples as blood, urine, or sputum, E will be of the order mV (1 mV = 0.001 V). In biological systems, a number of feedback systems tend to keep E within narrow limits, making pH and rH_2 interrelated and mutually dependent. This can be seen if we rewrite equation 9 to read:

(10) $rH_2 = 0.033\ E + 2pH$

If a biological system wants to keep E within certain limits, this implies that when rH_2 increases, pH will follow and visa versa. This is verified by BE-T-A measurements. One may view this in a teleological manner: by keeping E within certain limits and adjusting pH to rH_2, the body achieves the following—in a milieu with oxidative stress, the various fluids increase their amount of protons (pH goes up), thereby creating more protons to neutralize excessive electrons. Also, the excessive protons create a more intense magnetic field that can be regarded as an effort to promote self healing.[20,p.94-96]

R: The Dielectric Factor:

The third parameter, resistance R, is to calculate the flow of electrons. Knowing the Red-Ox potential E and R, one can calculate the flow of electrons I: the electrical current:

(11) I (calculated) = E (calculated) / R(measured)

R is given in the unite Ohm (Ω) and was formerly named ρ (rho) in France. It is internationally known as the "di-electric factor." It expresses the degree of ionization of a fluid under the influence of an electrical force.

R is dependent upon the presence of electrolytes in a fluid. In blood, the major players are natrium (sodium), which provides 92% of all positive electrolytes; chlorine provides 68% of all electrolytes. In practical situations, measurement of R is done with electrodes that are calibrated in a 0.1 mol KCl, corrected according to temperature.[32] Having these four entities we have a knowledge of free radicals, the acid-alkaline status, and electrolyte state. By doing enough tests on a number of healthy reference persons, using young sportswomen and sportsmen from France, Van Vincent, over a period of several decades, collected a database for the "ideal human being." He simultaneously compared these reference people to men and women of all ages with all sorts of diseases. Finally, he came up with revealing facts.

Table 2. Reduce energy and accumulation of acids in mesenchyme of 13 FMS patients.

N=13	pH	rH_2	R	Redox potential mV	Energy µW/cm_3
Blood	7.44	25	199	303.6	463.1
Urine	5.64	20.77	143	285	566.8

Measurements on Healthy People: Having established the technology, Van Vincent set out to do measurements to compare healthy people with diseased people. His data for healthy, young individuals are given in Table 1 below[21]

Table 1. Ideal measured values according to Van Vincent.

Fluid	pH	rH_2	R
Blood	7. 34 (7.10)	22.0	**Fluid pH rH2**210
Sputum	6.50	22.0	180 (140)
Urine	6.80	24.0	30

By the early 1950s, he learned that the two numbers in parenthesis typical of healthy young individuals. At that time, nutrition was more natural and drinking water less polluted.

It is thus interesting to see that venous blood in 2000 is more alkaline than 50 years back This indicates a decay in human capacity to excrete acids through the kidneys.[21] Sputum, which is an indication of the condition of intestinal secretion, tends these days to have a higher R factor. This is interpreted as meaning less ionized minerals in the intestinal secretion due to an overall lack of minerals in our present nutrition.

The Acidic Mesenchyme (the Structually Supporting Tissues of Organs). The use of Van Vincent BE-T-A technology opens an interesting option for clinical investigation into metabolic states of the human body. Going into detail about this issue would demand a number of extra pages, so we focus on what is of interest to the Lowe-thesis: the reduction of energy production in parenchyma (the productive tissues of organs), and the subsequent degradation of the mesenchyma (like connective tissues and lymphatic and blood vessels) that will lead to an accumulation of acids in it. Our findings and the interpretation of these findings for 13 FMS patients is given in Table 2.

The pH of venous blood and sputum taken from FMS patients is more alkaline than from healthy individuals.

From the statistical works of Van Vincent and others, we know that this is typical for advancing age, stomach dysfunction, nephritis, liver failure, cancers, intestinal symbiosis, and, relevant to the Lowe-thesis, chronic metabolic disorders.[35][12] Since none of our patients had diagnosed cancers, old age, or other such conditions, the test results are an indication of a chronic metabolic disorder. But what kind of metabolic disorder?

During the release of energy in chemical bonds, intracellular glucose is transformed to pyruvate. Pyruvate then enters the mitochondria. There it is converted to acetyl-Co-A, which enters the Krebs cycle and then the respiratory chain to produce ATP.

This process is strongly controlled by the thyroid hormone T_3, (liothyronine), along with necessary cofactors.[23] If the process of cellular respiration slows, pyruvate is transformed to excessive lactate, and the milieu becomes acidic. Surplus acids must then be buffered and transported from tissues to the blood.[24]

Direct measurements of pH using DMO and radioactive C have shown the following pH levels in healthy individuals: erythrocytes, 7.2; muscle tissues, 6.9; and the mitochondrial interior, 6.6.[25] During failing metabolic activity, these pH values fall to lower levels.

According to Elmau: ". . . so far it is legitimate to consider the blood as a mirror of the metabolic processes, as a reflection of what is happening in the mesenchyme (connective tissues) as a connecting link between the blood (itself a mesenchymal tissue) and the parenchyma."[25] However in degenerative processes, this relationship is not absolute, since the amount of acids produced in the connective tissues is no longer freely transported to the blood to be eliminated by the kidneys. Rather, it is stored in other mesenchymal tissues, such as connective tissues.[26]

According to Elmau, what happens is this: During excessive production of acids in the parenchyma, acids are stored and buffered in the mesenchyme, binding protons to potassium, sodium, and mucopolysaccharides. This condition is based on actual tests of mesenchymal (structural connective tissue) measurements in patients.[27]

Acidosis is partially compensated for in the mesenchyme, with some acid clearance. At the same time, however, the outward pumping of acids is reduced due to lack of ATP to support active mechanisms of acid transport. As a result, we do not get expected proportions of acidic venous blood; instead, *venous blood becomes more alkaline*, as seen among our FMS patients. More alkaline venous blood is thus a sign of longstanding mesenchymal acidosis. This is not to be confused with acidity of the arterial blood under similar conditions.

Long Standing Energy Failure. Complications develop when the buffering capacity of the mesenchyme is exhausted? The body then starts to take cations from the skeletal structures by increasing the activity of parathyroid hormone.[28] This again leads to a suppressed production of thyroid hormones as a way to save energy, thus reducing possible extra acidic load in the parenchyma. *The idea from nature's side seems to be to force the individual into a more idle life while trying to correct the misery of hypometabolism.*

However, the modern lifestyle fails its purpose. Instead of resting, pressured modern man and woman presses on, creating more mesenchymal acidosis.

This leads to a vicious circle: excessive acids are produced and stored in the mesenchyme, giving rise to a number of connective tissue problems such as pain, stiffness, and reduced muscle function. Over time, the skeletal system begins losing cations. On "the path to disaster," mesenchyme takes in Na^+ and H^+, thus worsening cellular acidosis. According to the degree of mesenchymal acidosis, the venous blood becomes more alkaline and the urine more acidic. In the extremes, we may find pH values of more than 7.5 for the venous blood and less than 4.5 for urine."[17]

This leads over time to K^+ deficiency in parenchyma. BE-T-A testing is actually more revealing of the K^+ deficiency than is measurement of K^+ in the blood.

Of clinical interest is that K^+ is shifted from the cell to the extracellular fluids to be used as a buffer for acids. When this happens, intracellular Mg+ is also depleted. We therefore end up with a mesenchymal acidosis plus K^+ and Mg+ cellular deficiency. This situation is often worsened by a deficient alimentary canal that misuses ACTH, cortisone, aldosterone, and diuretics.[29]

The presence of mesenchymal acidosis also leads to other shifts in BE-T-A readings. Typical is an increase in rH_2. This is to be understood as a compensatory mechanism to keep redox potential stable. As mentioned before, the Nernst redox potential is given by equation (9) $E = 30\ (rH_2 - 2pH)$. So when pH is rising, rH_2 increases to keep E somewhat constant. This leads to an increase in electron activity in the blood, causing more degeneration.

The urine readings indicate that FMS patients are excreting more acids. Even though acids are stored in the mesenchyme, some surplus is transferred to the blood, buffered, and then excreted in the urine. A measured pH = 5.64 clearly indicates an excretion of excessive protons. This reading indicates a twofold situation: excretion of excessive acids from the mesenchyme, plus a decay in kidney function, since healthy kidneys should always produce a pH= 6.8.[17]

Going beyond these basic considerations is of little clinical value in an introductory text such as this. My point is this: BE-T-A testing supports the thesis that FMS is indeed a loss of energy production in the parenchyma and a degeneration of the mesenchyma, as proposed by Lowe.[12] We therefore conclude, as did Dr. Lowe, that FMS, CFS, and hypothyroidism share the same underlying biochemical characteristic: too little energy is produced and distributed, and accordingly, cells work most of the time in an inefficient anaerobic mode.[17] In this mode, energy production (mostly ATP) is shifted from the high ATP-yielding mitochondrial respiration process to the less effective anaerobic glycolysis that results in accumulation of lactic acid.[23]

Forced to work under harsh conditions, the person's expenditure of energy is drastically reduced in a number of body compartments. This results in typical energy-depletion symptoms, such as tiredness, lethargy, slow pulse, falling blood pressure, cramping of peripheral vessels, lowered body temperature, loss of enthusiasm for life, loss of muscle tonus, and cramping of muscles.[17] Later, compensatory adjustments occur. These include the accumulation of fat tissue and mucous in the loose connective tissues for insulation against heat loss, reduced sugar metabolism, slowing of adrenal function, and loss of immune competence.[47]

Mitochondria: The Core of It All? It is common knowledge today among researchers and doctors that the core of this situation rests with the functioning of the cellular energy-producing units—the mitochondria.[30]

The mitochondria have been underrated in the history of medicine, ever since the discovery of their important function as cellular energy producers.[31] Few researchers have taken advantage of their dysfunction to explain clinical problems.

Three exceptional researchers (Warburg, Seeger, and Eck) should be mentioned. First is German Nobel Prize winner Otto Warburg, who in 1936 discovered an underlying common trait of all cancers.[32] He found that tumor cells had lost their ability to produce energy by respiration; instead, they went into a state of fermentation.

Later, German scientist Paul Gerhard Seeger discovered that the cause of this state of fermentation was impaired—even lost—mitochondrial respiration. The reduced respiration forced cells to extract ATP from glucose by the highly inefficient process of glycolysis.

Seeger also impressed the German-speaking world by conducting the largest number of lab tests on cancerous animals done until this date. He examined more than 100,000 lab animals over a period of 50 years. From his work Seeger concluded: not only is Warburg's discovery correct; *all* cancers produce little energy. Cancer can also be completely healed by sufficiently activating energy production. The nucleus of it all is the energy-producing activity of mitochondria.[33]

Seeker was never awarded the Nobel Prize for his cancer cures. This was due to one simple fact: he came from the wrong place—East Germany, a country not supported by the medical elite in the West.[34] He also did not have access to the high-tech biochemical products in the West.

He achieved most of his healings by using natural substances known as "antioxidants." Such substances stem from fresh fruits, berries, vegetables, trees, pollen flowers, and certain unicellular organisms. In Germany, these are known as "hefe." All hefe have common qualities: they are non-toxic and neutralize free radicals, which are toxic to cells. Hefe have a high content of enzymes, minerals, and vitamins known to be crucial cofactors for enzymes of the mitochondrial respiratory chain.[35]

According to Seeger, cancer is a problem of local cell energy production. Healing is but restoring respiration and the local electromagnetic milieu.[36] Later, several other researchers came to the same conclusion regarding other diseases.

Toward the end of the 20th century, masses of data accumulated that confirmed a related conclusion: without proper energy production and control, the functional capacity of cells starts to diminish. As capacity lessens, life as we like to live it also diminishes, and people eventually come to suffer from a number of depletion syndromes.[37]

Paul Eck: The Bio-holography of Metabolic Control. Today, a major contribution to the realization expressed in the section above is to be found in the life work of American lab-scientist Paul Eck. Over a 40-year-period, he tested several hundred thousand patients in his lab in Phoenix Arizona. From these tests, he came to realize that diseases in general are equivalent to reduced energy production and control. His conclusion lifted the eye from the mitochondria itself to the *hormonal control* of mitochondrial energy production.[37]

The work of Eck, his contemporary Hans Seley[38] ("father" of the moniker we call "stress"), and George Watson[39] have firmly established a fact: mitochondrial activity is the basis of life. These researchers also established that supplying mitochondria with proper "food," oxygen, and water, and regulating their supply according to the demand imposed on them and their capacity lies in the neuro-hormonal control system of the human body.

This system was termed the "holographic"[49] system by Eck. By this term, he meant that each part in the energy-producing system consists of a number of equally important players, each acting under one common law: produce enough energy at all times to sustain the maximal output of the person; or, if not, shut down production to protect misuse.[41]

The process of providing maximum energy output is the stage of stress. In response to excess stress, a number of well-defined stages shut down energy production. The shutdown leads to many processes that doctors give names called "diagnoses."

This brings us to a core issue of this paper: the history of the mitochondria has been utterly neglected, and the control of mitochondrial energy production has accordingly been given little thought. Thus, when a researcher like John Lowe rediscovers this fact and relates it to his favorite diagnosis, fibromyalgia, the medical elite are dumbfounded and at a loss for how to meet the challenge.[42]

To put the Lowe discovery (or, should one say "revival of a noble tradition") to the test, I used what knowledge I derived from his splendid book[12] and combined it with my roots in the European French-German tradition of men like Enderlein, Warburg,[43] Seeger,[34] Van Vincent,[45] and the American Broda Barnes.[46]

Keep asking the patient and you will get many answers. Keep asking the doctor and you will only get one word: the diagnosis. ● *Russian proverb*

PART III: THE CLINICAL PICTURE

Metabolism: Collecting Relevant Data. The first step in my testing of the Lowe discovery was to find a suitable clinical definition of hypometabolism. Such definitions exits in the form of statistics from researchers like Means, de Groot, Refetoff, and others.[47]

These researchers' statistics were based on a careful questioning[47] and observation of patients who hypometabolic patients in their blood samples. The patients therefore got the diagnosis "hypothyroidism," or deficiency of thyroid hormones.

Table 3: 27 women with FMS versus 177 cases of hypothyroidism from two studies

	FMS patients	Hypo patients		FMS patients	Hypo patients
Heart &circulation			C4: Coarse skin	44.4%	84%
H1: Low BBT	Too few answers given	100%	C5: Stiff / brittle hair	37.0%	75%
H2: Feeling cold	74.1%	92%	C6: Loss of hair	37.0%	49%
H3:Cold skin	66.2%	82%	C7:Brittle nails	44.4%	41%
H4:Dyspnoe	40.7%	64%	C8:Joint pains	81.5%	29%
H5:Paresthesia	66.7%	56%	**Muscles**		
H6:Peripheral edema	51.9%	56%	M1:Easily fatigue on exercise		
H7: Heart palpitation	63.0%	27%	M2 Muscle weakness	96.3%	61%
Emotional &mental functions			M3: Muscle-pain	96.3%	36%
E1: Failing memory	74.1%	65%			
E2: Depressed	77.8%	60%	**Vitality signs**		
E3: Restless/nervous	74.1%	43%	V1: General weakness	88.9%	99%
E4: Loss of appetite	14.8%	43%	V2: Lethargy	77.8%	88%
E5: Restless sleep/insomnia	81.57%	25%	V3: Weight gain	59.2%	68%
Connective Tissue			V4: Loss of sex drive	Too few answers given	50%
C1: Dry skin	63.0%	88%			
C2: Swollen eyelids	44.4%	88%			
C3: Swollen face	51.9%	87%			

However, the patients could also have lacked adequate production or effect of other hormones, such as insulin and parathyroid hormone. But due to the thinking of the time, only thyroid hormones levels were measured.[48]

Presumably lacking enough thyroid hormones, these hypometabolic patients developed a number of characteristic complaints. In Table 4, these symptoms and their frequency amongst the sufferers are noted. In Table 3, the incidence of symptoms among my FMS patients are compared to those of 177 hypothyroid patients.

These numbers clearly speaks for themselves and give a good picture of what it means to be hypometabolic and have "too little energy."[49]

Table 3 is adopted from the statistics of de Groot, Larsen, Refetoff, Stanbury,[69] and Broda Barnes.[12,p.255-256] Mean numbers arise by adding the various statistics and averaging the numbers. Arrangement of the symptoms and signs under the various headings is the author's own and can be debated, but these have proven useful for practical purposes. The "basal body temperature" test popularized by Broda Barnes consists of the patient putting a thermometer into the axilla before getting out of bed.[12, p.255-256] This test is debatable since many conditions may lead to reduced temperature under the arm. However, nearly 100% of all cases of hypothyroidism show low temperature before starting proper thyroid hormone therapy.

"Science is built on the premise that Nature answers intelligent questions intelligently. So, if no answers exists, there must be something wrong with the question."
● Nobel Laureate, 1972: Albert Szent-Györgyi

RESULTS

PART IV : DATA: ASKING THE INTELLIGENT QUESTION

Putting Patient Data into the Hypothyreot Table 3. Table 3 gave me a form by which I could identify hypothyroid symptoms among FMS patients. With this form, I started to collect data on FMS patients regarding the following "Leit-criteria": widespread muscle pain and tenderness, muscle fatigue and weakness, lethargy and asthenia, and signs of hypometabolism.

I asked every patient to fill in the hypothyroid questionnaire. Over a period of 2 years, more than 100 patients filled in the form. Some filled in the questionnaire by themselves in their homes after a first consultation where every question was explained. Others filled in the questionnaire at their initial meetings in our office.

The semantics of each question is explained in Appendix II to make clear to every colleague what meaning we gave each phrase.

In November 2005, we collected all the handwritten questionnaires. We found 56 questionnaires with symptoms of hypothyroid symptoms, plus complaints of muscle pain, tenderness, and muscle fatigue.

Of these 56 patients, 27 had diagnoses of FMS made by specialist before coming to our office. Of the remaining 29 patients, 12 had either myogenic encephalopathy/chronic fatigue syndrome, and the other 17 patients had myalgic symptoms plus general health problems that could easily fit a FMS diagnosis. However, this 29 patients had not been diagnosed by a qualified specialist; so to avoid accusations of being "too eager to see the light," these 17 patients were not included because they were waiting to have their diagnosis verified by a rheumatologist. (The wait was long in that there are only 2 among a population of 120,000 inhabitants in my country, a southern/damp/foggy region of the coastline already overloaded with rheumatic cases).

Of the 27 clear FMS cases, there were additional interesting diagnoses described later in this article (see Table 5). Of the 27 clear FMS cases, 7 patients had a history of thyroid gland disease and were currently on Levaxine (T_4) and/or liothyronine (T_3) medication. These patients were obviously under medicated. This was clear in that they all had symptoms or signs of hypothyroidism according to the percentages in Table 4.

Without being "too eager" to prove the point, it is of interest for all to notice that of the 27 female FMS patients, 7 suffered from under-medicated hypothyroidism. It is astonishing, however, that according to the laboratory (their blood samples of TSH and FT_4) and by their respective doctors' judgement, they were "adequately treated." Some 99% of doctors in my region believe the lab tests to be "sufficient testing for evaluating the problem."

Twenty-seven Patients with Classical FMS. Every questionnaire was now transferred to an Excel data program, and each entry matched with the journals of each patient to ensure 100% correctness—a procedure which lasted for one full month to ensure every entry to be 100% correct. All 56 patients are thus electronically stored. From this databank we extracted the 27 patients (the whole database was sent to the publisher for statistical analysis since there are more relationships to extract for future articles).

When asked about their symptoms, patients were not only asked to state if they had a specific symptom, but also to what degree it bothered them. The use of a subjective scale is not one of absolute unbiased measurement, but rather how the mind ranks a certain physical problem in a given situation where various sensations are weighed against each other. How this weighing is done is far from clear. It seems to me, however, that at least the importance of a certain body function is judged according to its necessity to perform. For example, as will be seen below, in the mind's experience of symptoms, those of muscle, joint, and cognitive dysfunction always come out high.

Each symptom (read experience of dysfunction) was ranked according to a simple 4-point scale (see "APPENDIX II. QUESTIONNAIRE SEMANTICS" below).

In the questionnaire, patients wrote the severity they found appropriate, between 1 and 3. The entries were added and averaged: Intensity $=\sum.I(j)/27$ where $j = 1, 2... 27$. (see Table 4). This formula gives a fair number for how intensely a certain symptoms was experienced by the group as a whole. The best picture, of course, would be to present a histogram for each entry, which will be done in a later article dealing with how CFS, FMS, FMS with hypometabolism and hypothyroidism with diffuse muscle pain compare.

Table 4. 27 Women with verified FMS from specialist.

Symptom	Frequency	Symptom Intensity	Symptom	Frequency	Symptom intensity
Heart &circulation			C4: Coarse skin	44.4%	0.70
H1: Low basal body temperature	Too few answers given	-------	C5: Stiff / brittle hair	37.0%	0.59
H2: Feeling cold	74.1%	1.48	C6: Loss of hair	37.0%	0.56
H3:Cold skin	66.2%	1,29	C7:Brittle nails	44.4%	0.67
H4:Dyspnoe	40.7%	0.74	C8:Joint pains	81.5%	1.59
H5:Paresthesia	66.7%	1.15	**Muscles**		
H6:Peripheral edema	51,9%	1.15	M1: Easily fatigued on exercise	Implicated in M2-see appendix	
H7: Heart palpitation	63.0%	0.93	M2: Muscle weakness	96.3%	2,26
Emotional &mental functions			M3: Muscle-pain	96.3%	2.48
E1: Failing memory	74.1%	1.52			
E2: Depressed	77.8%	1.37	**Vitality signs**		
E3: Restless/nervous	74.1%	1.40	V1: General weakness	88.9%	2,07
E4: Loss of appetite	14.8%	0.11	V2: Lethargy	77.8%	1.81
E5: Restless sleep/insomnia	81.57%	1.63	V3: Weight gain	59.2%	1.14
Connective Tissue			V4: Loss of sex drive	Too few answers	
C1: Dry skin	63.01%	1.15			
C2: Swollen eyelids	44.4%	0.78			
C3: Swollen face	51.9%	0.96			

As seen in Table 4, the average FMS patient had a symptom pattern the same as a hypothyroid patient untreated with thyroid hormone supplements.[50] Any endocrinologist who would read the statistics in Table 4—if not knowing the diagnosis his colleague the rheumatologist would give—would probably diagnose all these patients as hypothyroid. As will later be revealed, 7 of these patients were indeed found to suffer from thyroid disease. But, again, most of these of these patients got an FMS diagnosis before it was discovered that they also had a thyroid disease.[51] And even more interesting: all of these patients got symptomatic improvement from their FMS symptoms when they received adequate amounts of thyroid hormone (levaxine and liothyronine). And even more interesting, 2 of the hypothyroid patients had to take supraphysiological doses of thyroid hormones as judged by current laboratory standards.[52]

Visa versa: the remaining FMS patients who were not diagnosed as having hypothyroidism, all improved from their FMS when they received therapy that improved their metabolism. The 2 patients who received traditional psychoactive drugs showed very little benefit from such medications as to the majority of neuromuscular symptoms.

The reason that muscle pain frequency amongst the 27 FMS sufferers was not 100%, was due to one particular patient: a 36 year old women who was cured from her muscle pain before entering the study.

Of all the data, one special relationships stands out as being of most interest: In true hypothyroidism due to thyroid gland failure, loss of vitality is not reflected by an abnormal rise in insomnia/sleeping pattern abnormality. But among FMS patients, complaints of insomnia rank of the same order as loss of vitality. This could indicate that loss of vitality in a FMS patient could be due to restless sleep due to muscle pain.

Additional medical diagnoses at time of first contact. Except for the patients who received their FMS diagnosis from a qualified specialist in rheumatology, the diagnosis for each patient is a question of medical attitude. Most of the patients, including those with clear-cut FMS diagnoses, had a "host of problems." Most of the patients' doctors underrated the other medical problems and focused only on the patients' major symptoms. See Table 5 for other diseases identified.

Currently Available Laboratory Testing. We used the lab tests available in Norway at the time,[53] but we screened all patients for their metabolic status. For those receiving thyroid hormones from their doctors, thyroid lab tests were all "within the normal range."

However, two patients suffered from untreated overt overt hypothyroidism at the time of contact. Two others

Table 5: Medical status at time of first consultation

Medical information	Numbers
Average age	49.5 years
Med-requiring cardiovascular disease	3
Central nervous system dis., except ME	1
Med-requiring psychiatric disorders	2
FMS previously confirmed by specialist	27
Subclass (a) simple case of FMS	15
Subclass (b) FMS + hypothyroidism	7
Subclass (c) FMS+ ME or CFS	3
Subclass d) FMS + diabetes	2
Immunity/allergies (i.e., colitis or asthma)	6
Patients on thyroid medication	7
Patients on cortisone	2

previously undiscovered subclinical hypothyreoidism were also discovered. Because she was "forgotten by the system," one of the hypothyroid women was left untreated by her doctor for 20 years!

The remaining patients all had perfectly normal, "within the reference range," levels of FT_4, FT_3, TSH, and rT_3.[54]

Microbiological Analysis. In trying to find causes for patients' FMS and their obvious hypometablic states, we also tested all for antibodies against five microbes: Epstein Barr Virus, Cytomegalovirus, Chlamydia Trachomatis, Mycoplasma, and Borrelia Burgdorferi.

This testing revealed three cases of chronic, undiagnosed Mycoplasma infections.[55] All patients were treated with Doxyllin 200 mg per day, plus antioxidants and probiotic bacteria cultures.[56] All three patients are currently under therapy for the 5th month and improving.

Metabolic Status by Use of the Van Vincent Method. Recapturing the data in Table 2, we note the BE-T-A measurements of 13 FMS patients. If one analyzes venous blood and compares it with the "ideal," the patients had slight oxidative stress. (Remember that although the breaking point for water is $rH_2 = 28$, for blood it is $rH_2 = 22$.) pH is alkaline when R is slightly elevated. The ideal R for women is 190 and for men is 220. (The latter is often given as the ideal in many textbooks on BE-T-A).[57]

The data in Table 2 indicates that the FMS patients had mesenchymal acidosis. This is part of the tissue terrain that Van Vincent often called "the terrain for degenerative diseases" or "diseases of modern civilization." In this part of the terrain, one also finds increased risks for cancers, viral infections, thromboses, and cardiovascular diseases.[58]

Urine is highly acidic due to the excretion of excessive acid from the mesenchyme. Acidic urine occurs because there is no blocking of acid transport from mesenchym to blood, and rH_2 is a very low indication of holding back electrons from the process of proton excretion.

The FMS patients' urine R is remarkably high: 143 versus an ideal of 30. This high R indicates excretion of mineral ions in the process of pH–rH_2 regulation. Mineral deficiency is to be expected in the long run.[58]

Finally, the acidity of the patients' sputum was low. Sputum is an indication of the function of the digestive system, with low acidity indicating less effective digestion. The low rH_2 indicates a reduced milieu with a possible excess of free radicals (electron-grabbers). In addition, the high R indicates mineral deficiency.[58]

"Our bodies are energy-producing machines. Every aspect of health depends on adequate energy generation. ● Lawrence D Wilson, MD

CONCLUSION

PART III: SCIENTIFIC HYPOTHESIS IN SUPPORT OF DR. LOWE'S THESIS

Reduced Effects of Hormones: the Culprit? Collecting our own data and those from a number of reliable sources we can conclude:

(1) All FMS patients, when thoroughly questioned and examined, have a clinical picture with a high degree of similarity to those of hypometabolism, as caused by a deficiency of thyroid hormones. Actually, in speaking of this clinical picture, it is necessary to speak in the *plural*, since we refer to clinical *pictures*—not just one fixed picture.

But despite having degrees of differences between patients' clinical pictures, the patients still belong to what in the mathematical theory of patterns is called "of the same class."[59]

(2) When investigated, our 27 FMS patients fell into two distinct categories: first, those who did indeed have thyroid hormone *deficiencies*, as judged by current laboratory standards; and second, those who were clearly euthreot (their TSH and thyroid hormone levels "within their reference ranges") but still had the same clinical picture of untreated hypothyroid patients and were clearly hypometabolic.

Approximately 34% of FMS patients fell into this latter category, by J.C. Lowe's calculations from the studies available in 2000.[85] (Garrison and Breeding credited Lowe's research, but argued that the percentage of euthyreotic FMS patients who recover only with thyroid hormone therapy is substantially higher.[91]) Lowe also calculated that 55% of FMS patients had either primary or central hypothyroid. From the evidence of Sweden's Bo Wikland, the remaining 11% of FMS patients—or perhaps a much higher percentage—could have hypothyroidism not biochemically diagnosable because of their "normal" TSH, FT_3, FT_4, and antithyroid antibody levels. Among these patients, an accurate diagnosis of autoimmunity can be made only with fine-needle aspiration cytology.[88] Wikland found that 40% of 219 chronic fatigue patients with autoimmune thyroiditis had reference range TSH, FT_3, FT_4 levels. Only half of these patients had high antibodies.[89][90]

(3) With the majority of FMS patients, there was no sign of reduced production of thyroid hormones (except for those who had the combination of FMS plus hypothyroidism). Also, there was no indication of impaired transport of hormones.[64]

Adding up these premises, among the euthyreot FMS patients, the most plausible conclusion is that there must be a reduced effect of thyroid hormones at the cellular level. This reduced effect could be due to any of several factors. For example, transport might be impaired across the barrier between the blood and the intercellular fluid between cells, where hormones are transported by colloid mineral-complexes to the cellular membranes. From there, the hormones are shuttled across membranes into cells by pinocytosis, where they are carried to the nuclear membrane and attached to enzymes that rearrange T_4 into 4 possible isomers of T_3. Only 3 of these isomers are effective. The fourth, known as reverse-T_3, is an inactive variety that seems to hinder the effect of the other three effective isomers.[60]

The three active isomers all belong to a family of hormones known as cell-membrane structural rearrangement hormones. These hormones attach to receptors on the DNA. The attachment causes certain genes to start transcription for production of the real powerhouse of the cell, the small energy factories called "mitochondria," and the host of enzymes that catalyze reactions within the mitochondria.[61]

Each step in this process is vulnerable to changes in the local milieu and in the availability of certain cofactors, such as minerals, vitamins, and free fatty acids. If some of these cofactors are deficient, even sufficient thyroid hormone will not produce energy in the form of active ATP.[61]

Mitochondrial Energy Production. Once it is realized that mitochondrial energy is the major source of biochemical energy—and a seemingly infinite supply of it—the clinical picture gets simpler. It is not possible to understand these matters unless the medical society makes an important shift in its mindset: from the gross (clinical) to the subtle atomic world.

According to late Nobel Prize winner Szent György, future medicine will work on the atomic level, and everything will be explained from there. We are now in the age he spoke of some 60 years ago upon receiving his Nobel Prize for the co-discovery of one of the major atomic steps in medicine: the ability of ascorbic acid (vitamin C)—which can be properly understood *only* on the atomic level—to deliver free electrons to the energy producing machinery of the cell, the mitochondria.[62]

The mitochondria are the engines of the cell. Small bacterial-like structures, they are believed to be the primitive ancestors from a species of bacteria known as E-Coli.[8] They can reproduce within themselves from their own limited genome, but their genomic source is part of the DNA structure in the nucleus of the cell.[64] The thyroid hormone T_3, amongst other factors, activates the genes that transcript instruction to make more of these "energy producing animals," increasing their numbers.[65]

Inside the mitochondria's double-layer lipid membrane, acetyl-CoA produces active ATP through a series of steps known as cellular respiration. The source for this raw material is either fatty acids or pyruvic acid from the decomposition of glucose in the cytosol of the cell. Outside of the mitochondria, these breakdown products yield only small amounts of active ATP.[65] Once inside a mitochondria, however, acetyl-CoA from free fatty acids or from converted pyruvic acid enters a transformative process known as the "citric acid" or "Krebs cycle." This cyclic transformation of citric acid (from acetyl-Co A) produces a highly energy-rich molecule known as $NADH_2$. What has happened is that enormous electrical energy has been ripped off from the various molecules in the citric acid cycle and has been stored in the chemical bounds of the hydrogen atoms attached to ionize NAD^+, forming $NADH_2$.[67]

The newly-produced $NADH_2$ is then sent to a number of small molecules on the inner wall of the mitochondrion, known as "cytochromes." There, the energy-rich electrons in the $NADH_2$ are taken away and transported to a chain reaction that produces active ATP from its precursor, ADP.[52] The phosphate bonds in ATP now hold all the electrical energy once stored in $NADH_2$, and ATP travels out of the mitochondrion to supply cellular chemical activity with life-giving electrical energy.[12,pp.165-166] The protons released when the electrons are transported away eventually combine with oxygen and form water. The need for oxygen as a cofactor to the protons gives name to the process: "cellular respiration."

I cannot emphasize it strongly enough: mitochondrial respiration is all about taking electrical energy from nutrients (sugar and fatty acids) and putting it into smaller molecules called ATP. ATP can then move freely and support all other life processes throughout the body's cells. Basically energy is about electromagnetic energy: the energy is either (1) trapped in chemical bounds, (2) freely moving or rotating ions or electrons, or (3) pure electromagnetic energy waves. Beyond that, there is no other source of energy in the human body.[68]

Mitochondrial Nourishment. Like any being, unicellular or multicultural, mitochondrial life is sustained the "traditional way": nourishment enters, energy is released, and waste products in the form of protein-bound toxins are excreted in the process.[69] There is no mystery to this, only intense interest of the curious mind. However, not even the most authoritative textbooks from the medical establishment contain a single word about the necessary cofactors in the mitochondrial respiration process, nor anything otherwise about the mitochondrion's nourishment and toxin production and elimination.

This omission is so glaring that it blinds the eye, which this author personally believes is an intended effect. The intention is to mislead the medical society into believing that energy is produced just from sugars, proteins, and fatty acids. Some textbook authors, however, believe fatty acids to be "dangerous," and, to be politically correct, they therefore do not even mention the fatty acids.[70]

However, there are a number of laboratories and experts on nutritional medicine that do indeed test for and include the nutrients necessary to make sufficient energy available to cells. A good and recommended source of information is a U.S.-based company, US Biotek. Through this company, one can get a listing of life sustaining nutrients known to be necessary for enough energy to be available to cells. Briefly, these nutrients are:

Krebs Cycle:

1. Vitamine B complex
2. Coenzyme Q10
3. Alpha lipoic acid
4. Aspartic acid
5. Alpha keto glutarate
6. Several amino acids (L-phenylalanine, L-arginine, L-isoleucine, L-valine, L-gutamine, L-cystein, L-tyrosine, L-hydroxytyptophan , and N-acetyl-cystein)
7. Minerals (copper, ion, magnesium, manganese
8. Necessary antioxidants (i.o.w: electron-donors) vitamin C, E, and alpha lipoic acids

(For a complete list of mitochondrial nutrition and metabolic testing: contact US-BioTek, 13500 Linden Avenue North, Seattle, WA 98133 also www.usbiotek.com.)

These substances cover only what is needed inside the mitochondria. The work of Berlin's Paul G. Seeger as a research scientists for over 50 active years proved beyond doubt: if essential nutrients are missing, or if electron donors are lacking, mitochondrial respiration suffers, and the production of ATP "sinks like stone." This results in hypometabolism and eventually cancer.[70]

Seeger also showed beyond doubt that the presence of toxins (free radicals) either damaged the cell membranes or disrupted the chemical processes inside the cell. In either case, this also leads to same results: hypometabolism and finally cancer.[70]

PUTTING IT ALTOGETHER

It is now due time to put together the data I have included here. The point is to try to make a synthesis that leads to some basic understanding. I have done so in a series of short statements.

1. The clinical pictures of FMS and hypothyroid patients are similar: Comparing the clinical picture (symptoms + signs + objective findings) of FMS and hypothyroidism, one find them to belong to the same class of phenomena. This means that if a doctor is given the clinical picture of a FMS patient with no diagnosis attached, he will in most cases label the patient "hypothyroid."[71]

2. FMS patients have mesenchymal acidosis: The Van Vincent BE-T-A test shows that FMS patients belong to a special class of patients; those who have mesenchymal acidosis. This means they have an accumulation of acids in their connective tissues. It also means that unless the patient is actually poisoned by an external acid, his or her parenchymal metabolic rate is reduced, and that, as a result, lactic acid and free radicals are accumulating in his or her connective tissues.[72]

3. Blood sample: results show two etiological subgroups: When investigating blood samples, we discovered at least two major subgroups of FMS patients: (1) a euthyreot group with no signs of failing thyroid production or transport; (2) another group suffering from a variety of thyroid disease states, such as thyroid hormone deficiency. In general, both groups of patients get simultaneous relief from FMS and any thyroid problem when they receive "enough "thyroid hormone" (meaning, enough to alleviate their symptoms and normalize their metabolism). The former groups of patients, however, may need additional help, such as supplemental cofactors, to restore thyroid hormone effects.[19]

4. Both subgroups deserve the same label: hypo-

metabolic states: A reduced level of thyroid hormones or hindered cellular effects of the hormones both produce the same impact on patients: clinical hypometabolism and mesenchymal acidosis that is typical of mitochondrial failure. We discovered no major difference between the two groups.

Mitochondrial failure explains the acidosis. When glucose is not broken down to acetyl-CoA and transformed to ATP in the Krebs-cytochrome respiration chain, what is produced instead is lactic acid. Mitochondria failure also produces free radicals, and both of these processes explain parcencymal acidosis and subsequent mesenchymal acidosis.[16]

5. Loss of mesenchymal electrical properties: To buffer acids, potassium and magnesium are lost from cells to the mesenchyme. Sodium, on the other hand, enters cells and weakens the electrical potential across the cells' membranes. This leads to further mitochondrial failure. In the later stages, calcium is extracted from the skeletal system to buffer acids. This is in accord with the clinical findings of J.C. Lowe who reported an increased need for calcium and magnesium in FMS patients.[12] Potassium is not mentioned, probably because this mineral is abundant in the daily food, while calcium and magnesium are not.[103]

6. Need for more thyroid hormones: To correct patients' symptoms and signs, more thyroid hormones are clearly needed, together with minerals, vitamins and other cofactors to balance the electrolytes (see patient 5) and nourish the mitochondria.[76] At the same time, one needs to find the cause(s) for cellular resistance (such as microbes, toxins, and heavy metals) and try to remove these.

What is the "chicken" and the "egg" may in the end be a matter of philosophy. Clinically, both ends should be dealt with: the lack of hormones and/or any causes of the failed cellular mission of the hormones.

How it all should be dealt with is according to the understanding of the doctor and the unique condition of each patient, not to forget the possibility of making corrections within the framework of the medical establishment.

POLITICAL POSTSRIPT: A DISCOVERY WORTH PROMOTING IN NORWAY

As this article is being written, the author is currently working to get the Lowe thesis known amongst colleges. This has proved to be somewhat problematic.

The reason is that in Norway, doctors are compelled to adhere to a doctrine: metabolism is best understood in terms of the "normal range" of TSH, T_3, and T_4. As long as these measurements are within their "normal ranges," metabolism is OK, and patient complaints should be ascribed to psychosomatic factors. In one particular case the author was even "reported" to the authorities for giving a different opinion, that of "euthyreot hypometabolism."

On the brighter side is the fact that some doctors now seem to be catching up with the idea of eurthyreot hypometabolic syndromes and functional thyroid hormone resistance. Fortunately, Aker University Hospital in Oslo, known for its work on hormones, has met the idea with a positive response.[77]

Personally I have found these ideas and discoveries so useful that I have decided to use the rest of my career to go deeper into the relationship between energy production, hypometabolism, and degenerative diseases. Therefore, I express a heartfelt thanks to the pioneer John C. Lowe and to the journal *Thyroid Science* for publishing my findings.

APPENDIX: THE ENERGY VIEWPOINT

"*All medicine is energy medicine*." ● James Oschmann

"You cannot solve a problem unless you have an outcome." ● Joseph O`Connor[1]

The Lowe discovery that FMS and CFS are indeed hypometabolic syndromes may well be one of the major breakthroughs in modern clinical medicine. There are others, of course, who independently have made the discovery that most diseases may be viewed as a failure to produce and distribute enough energy. Examples are Paul Eck, George Watson, and Szent György. But the work of John C. Lowe is the first major work to nail a specific disease entity outside the ordinary endocrinological diseases to metabolic failure.

The morphological orientation, or what could be called the 19th century medical paradigm, is that a "disease" is something static and unchangeably recognized by the presence of a "list of symptoms, signs, and findings."[78] But once we enter the realm of metabolism, we are in for a change of paradigm; we move from a medical science of morphology to a science of energy. The core of metabolism is the production of energy and its distribution and use.

Once entering the realm of energy, medicine enters the realm of physics where scientists have for 200 years recognized the fact that phenomena are changing. The search is thus not for something static but for underlying laws of nature that make things happen. Physical science is thus occupied with principles and expects natural events to be in movements all the time.[107]

The search for natural laws has been the source of success in the physical sciences. Technology in general is far more advanced today in many respects than in medical science, which is somehow, for better or worse, stuck in static 19th-century thinking. The gulf between the two worlds can be pictured like this: It is 39 years since U.S. scientists and technocrats put a man on the moon for a fraction of the cost of what is spent on cancer research and treatment per year in the U.S. Despite this fact, there are still few medical cures for cancer and no sensible explanations for this failure of established medicine.[80]

This situation is not due to a lack of brilliant medical scientists, lack of enthusiasm, intelligence, good intentions, or brave efforts. It is due simply to this: GPs, by which the community of good men navigate, continue to point to a path of struggle and toil through a barren landscape.[81]

Only by change of path will more fruitful landscape be found; and this is what John C. Lowe has done. By asking the right questions, he has single-handedly loaded the scientific GPs with a path that has entered the realm of the physical sciences. This realm is based on energy thinking and the search for underlying laws of nature. Instead of looking at snapshots, one is watching a film and asking for the ways the film's director is "thinking." This orientation is called "functional medicine" or "energy-based medicine." It by no means excludes chemistry or morphology, but rather encompasses these as *part* of the curriculum, rather than the end of all thinking.[82]

By doing this, John C. Lowe has followed the path of great American scientists such as the "father of stress," Hans Selye, nutritionalist George Watson, mineral researcher Paul Eck, biophysicist and surgeon Robert O. Becker,[83] and luminaries of the Old World such as Nobel Laureate Otto Warburg, cancer-researcher Paul Gerhard Seeger, Hungarian biophysicist and Nobel Laureate Szent Györgye, and many more who wanted to merge the powerful dynamic thinking of physics with the wealth of morphological knowledge of medicine.[84]

It is my sincere opinion that understanding FMS and CFS as conditions of metabolic failure is like handing the GP with a new map to navigate turbid waters, and thereby to help patients and doctors alike to tread a better path of understanding, leading above all to a better outcome.

APPENDIX II. QUESTIONNAIRE SEMANTICS

0 = I do not sense this symptom/problem.
1 = I feel this is a small problem (of dysfunction). It is weak and gives me little trouble in my personal life.
2 = I feel this to be a medium problem. It causes me trouble, but I can manage to go along with certain compromises.
3 = It bothers me very much. I feel that it hinders me in my daily life, and I am bothered all the time by it. It is amongst the problems I need to reduce to be able to improve.

Answers depend on the questions asked. We tried to select a proper linguistic structure based on NLP-principles to reach clear answers. For readers interested in our linguistic structure, please email me at for a copy of the questions in the questionnaire: bjorn@dr-overbye.

REFERENCES

(For those who want to explore the domain deeper, I have provided in the list below some of the relevant literature and a few personal notes that are not included in the main text.)

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41. According to Watson and Eck, there will be a gradual decline in energy production if stress is allowed to continue unchecked. My own thesis is that the process is not one of decay, but is one of salvation. In this process, the body tries to save its own life by gradually shutting down energy-expenditure by gradually reducing energy production. The reduction begins with those systems that can initially be scarified, and goes on gradually until the most vital parts are in danger: the kidneys, brain, heart, and lungs.
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48. One of the major drawback of numerous researchers of hypo

metabolism in the past and in the present time is their focus on thyroid hormone alone. A number of thyroid books completely overlook the simple fact that the thyroid is but one of many hormones working to regulate cellular production of ATP. Two major steps forward are the work of John C. Lowe and Paul Eck`s at Ananalytic Research Laboratoium. In a forthcoming PhD thesis by our colleague Ragnar Wattøe on the nature of complex regional pain syndromes, the mitochondrial aspect is the central focus. The thesis is obtainable from the author: Dr. Øverbye, Boks 348 BN4803 Arendal, Norway.

49. This table is adopted from the book of de Groot, et al.[14] In the original work there are two statistics termed A and B (see full exposé in Lowe, J.C.: *The Metabolic Treatment of Fibromyalgia*, Boulder, McDowell Publishing Co., 2000, p.837). My numbers were achieved by taking the mean of the two: (A+B)/2 and rounding off to the nearest whole number, which is mathematically acceptable as long as the basis for the numbers are mentioned.
50. See reference 3. Much can be said about the work of Yunus. The basic problem with his work, however, is that he looked for a muscular disease, not for a metabolic syndrome. His diagnostic criteria therefore fit only a certain percentage of all hypometabolic patients suffering from muscle pain similar to FMS.
51. Simple logics tells us that if lack of thyroid hormones leads to a certain clinical profile characterized by symptoms S1,S2YsN, these symptoms together are what is called a mathematical Group, which we may call "A." If another disease entity has the symptoms S1,S2YsN, the symptoms can form a Group called "B." According to mathematical logic, if sj =Sj for j= 1,2,YN, then A = B. So, if hypothyreosis is classed as Group A, and FMS is classed as Group B, by simple logic one would end up saying FMS = hypothyreoidism. However, most FMS patients do not have abnormal blood levels of thyroid hormones, warranting classification A. Then the only logical explanation will be found in the fact that symptoms are not an expression of blood thyroid hormone levels. Instead, the symptoms arise from biological effects of the hormones at the cellular level. In other words, we deal with metabolism = the biological effect of hormones and their cofactors. For those who want to go deeper into the subject I recommendm Max Black: *Critical Thinking*, 2nd edition, Englewood, Prentice Hall, 1962. John C. Lowe is the only scientist I know of who has so far ventured into the use of logic in the diagnosis of FMS.
52. Many of my hypothyroid patients indeed got the diagnose FMS before getting the diagnosis of hypothyroidism, which is just another support for reference 33.
53. Lowe is one of the advocates of supraphysiological doses of thyroid hormones for FMS, when appropriate, to override cellular resistance to the hormone. Using supraphysiological dose of hormones is nothing new. For example, a number of conditions require this, such as hormonal replacement therapy in postmenopausal women, the p-Pill for fertile women, the clinical use of cortisone (sic) which in Norway is routinely given to even infants to relieve ordinary asthma.
54. The best biochemical metabolic testing available for Norwegian doctors at the present is the Aker University Hospital of Oslo.They can supply the following tests: TSH, FT_4,T_4,FT_3,T_3, rT_3,Tg, anti-Tg, anti-TPO, TRAS, PTH, Protein bound Iodid, DHEA, DHEA sulphate, cortisol, ACTH, aldosterone, complete sex -hormone screening, and ADH.
55. According to the County Medical Office (Fylkeslegen), using such tests on a routine basis to investigate hypometabolic problems is not common. According to the Regional Hospital in my County, the typical tests used on the hospital level are only the TSH, FT_3 and FT_4—and nothing else. The metabolic effects of thyroid hormone medications are evaluated by TSH levels alone. As long as the TSH level is within range, metabolism is considered normal. However correspondences with hospital doctors, patients, and general practitioners have revealed that 9 out of 10 are unaware that a TSH above 2.5 in the Unites States may indicate the beginning of metabolic failure. See www.thyroidmanager.com.
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POSTSCRIPT

It is a sad fact that FMS and a host of other diseases could be successfully understood, quantified, and treated with quite simple means. This could be accomplished were it not for the rise of a fragmentary and ever more specialized occupation known as current progress in medical science. In the end, this current "progress" will lead to nowhere, except each doctor living on a small island in an ocean of unintelligible data. The energy viewpoint can solve the diseases from which humans suffer gracefully and with beauty.

The author is presently conducting a longitudinal study of the hypometabolic states of FMS patients with BE-T-A testing. The focus of the study is the paradox of alkaline venous blood despite mesenchymal acidosis. This study will be finished by end of 2008.

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Screening for Thyroid Dysfunction in the Diabetic/Non-Diabetic Population

Palanisamy Pasupathi,* Govindaswamy Bakthavathsalam,*
Ganesan Saravanan, Ramachandran Sundaramoorthi***

*Institute of Laboratory Medicine, K.G. Hospital and Post Graduate Medical Institute,
Coimbatore-641 018, Tamil Nadu, India
**Department of Biochemistry & Biotechnology, Faculty of Science, Annamalai University,
Annamalainagar-608002, Tamil Nadu, India

Contact: Dr. P. Pasupathi, PhD drppasupathi@gmail.com

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Abstract. The objective of this study was to investigate the effect of diabetes mellitus on thyroid hormone levels and other biochemical variables. The study population consisted of 200 subjects divided into two groups: diabetic (n=100) and non-diabetic (n=100). In order to clarify the mechanism of impaired thyroid hormone levels in patients with diabetes, blood glucose, glycosylated hemoglobin (HbA1C), lipids, proteins, urea, microalbuminurea, thyroid stimulating hormone (TSH), total thyroxine (T_4), total triiodothyronine (T_3), free thyroxine (FT_4), and free triiodothyronine (FT_3) were examined. A significant increase in the levels of blood glucose, HbA1C, serum cholesterol, triglyceride, low-density lipoprotein (LDL-C), very low-density lipoprotein (VLDL-C), urea, creatinine, and microalbuminurea was observed in diabetic patients compared to non-diabetic subjects. On the other hand, the levels of total protein, albumin, and high-density lipoprotein (HDL-C) were significantly decreased in diabetics. The level of TSH was significantly decreased whereas the levels of T_4 and FT_4 were significantly increased in diabetic patients compared to control subjects. However, the T_3 and FT_3 levels did not differ significantly between groups. Out of 100 diabetic patients studied, 28% had low plasma thyroid hormone levels, 17% had high thyroid hormone, and 55% had euthyroid levels. This study has shown a high incidence of abnormal thyroid hormone levels among the diabetics. In conclusion, our findings demonstrate that detection of abnormal thyroid hormone levels in the early stage of diabetes mellitus will help the patients to improve quality of life and reduce the morbidity rate.

Keywords. Diabetes mellitus • Glycosylated hemoglobin • Thyroid hormones • Serum lipids

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Introduction

Diabetes mellitus is an important health problem affecting major populations worldwide. It is characterized by absolute or relative deficiencies in insulin secretion and/or insulin action associated with chronic hyperglycemia and disturbances of carbohydrate, lipid, and protein metabolism. Defects in carbohydrate metabolizing machinery and consistent efforts of the physiological system to correct the imbalance in carbohydrate metabolism place an overexertion on the endocrine system. Continuing deterioration of endocrine control exacerbates the metabolic disturbances and leads primarily to hyperglycemia.[1][2][3]

Epidemiological studies and clinical trials strongly support the notion that hyperglycemia is the principal cause of diabetic complications. Effective blood glucose control is the key for preventing or reversing complications and improving the quality of life for patients with diabetes. Thus, sustained reduction of hyperglycemia will decrease the risk of developing microvascular complications and most likely reduce the risk of macrovascular complications.[4][5]

A recent study by the World Health Organization (WHO) estimated that the worldwide prevalence of diabetes in 2002 was 170 million, with the number predicted to grow to 366 million or more by 2030. The adoption of a sedentary lifestyle, the consumption of non-traditional foods, and a genetic predisposition to the disease are thought to be the major underlying causes of the epidemic.[6] Despite great strides that have been made in the understanding and management of diabetes, the disease and its related complications are increasing unabated.

The influence of endocrine and non-endocrine organs other than the pancreas on diabetes mellitus is documented. Occasionally, other endocrine disorders such as abnormal thyroid hormone levels are found in diabetes.[7] The major alterations in thyroid hormone system are a reduction in the TSH stimulation of the thyroid gland, probably caused by central hypothyroidism, and in the peripheral generation of T_3 from T_4. In chemically induced diabetic animals, the alterations in the hypothalamo-pituitary-thyroid axis in diabetic rats are numerous. Hypothalamic and plasma TRH, pituitary and plasma TSH, as well as TSH secretion rate are all reduced, and the TSH response to TRH is decreased despite normal peripheral TSH metabolism. T_3 and T_4 production and iodide uptake by the thyroid are diminished. There are also important structural changes in the thyroid gland and pituitary that are accompanied by marked alterations in their secretory activity. In addition, T_4 deiodination to T_3 in peripheral tissues is decreased.[8][9] The physiological and biochemical interrelationship between insulin and the influence of both insulin and iodothyronines on the metabolism of carbohydrates, proteins, and lipids are recorded.[10] As Udiong et al. said, “Such records indicate that iodothyronines are insulin antagonists with high levels being diabetogenic, while absence of iodothyronines inhibits the development of diabetes.”[9] Since thyroid hormone abnormalities are frequently associated with diabetes, the present investigation was to assess the adverse effects of diabetes on thyroid hormone levels and other biochemical variables in diabetic patients.

Materials and Methods

Study Population

The study population consisted of 200 subjects (age- and sex-matched) divided into two groups: diabetic (n=100; 15 type 1 and 85 type 2) and non-diabetic (n=100). All the subjects under study were recruited from K.G. Hospital and Postgraduate Medical Institute, Coimbatore, Tamil Nadu, India, from January, 2007 to March, 2008. General health characteristics such as age, sex, smoking status, menopausal status, alcohol consumption, and dietary habits (particularly as related to preference) were investigated by a self-administered questionnaire. All the patients in the diabetic group were confirmed diabetics who previously had fasting blood glucose levels >120 mg/dL on more than two occasions, and who were receiving treatment such as insulin, glybenicide, glucophage, or physical exercise therapy for diabetes mellitus. The initial criteria used in separating type 1 from type 2 subjects were the physician classifications based on the age of onset of diabetes and dependence on insulin therapy alone to achieve normal plasma concentrations. We classified diabetics who met the above criteria and had fasting C-peptide levels of less than 3.8ng/mL as type 1. Diabetics whose fasting C-peptide concentrations were above 3.8ng/mL and who were responding to other therapeutic measures or agents were classified as type 2. This was based on a C-peptide reference range of 0.8-3.8 ng/mL that established using the same reagent kits for the 100 non-diabetic subjects of the same community.

Each diabetic and non-diabetic subject was physically examined to rule out thyroid disorders. In addition, none of the subjects had a history of previous thyroid disease. Age- and sex-matched healthy volunteers without a history of diabetes were considered to be control subjects. All subjects were informed about the objectives of the study and what roles they were expected to play. The study excluded very ill patients with complications of diabetes mellitus and those with a known history of thyroid dysfunction. All samples were specimens taken from subjects who fasted for at least 8 hours before the blood collection.

Classification of the values into high, low, or normal thyroid hormone levels was based on the following criteria. Subjects classified as having high levels of thyroid hormones had FT_4 values >1.6 ng/L or TSH<0.4 μIU/mL or both. Those classified as having low levels had FT_4 values <0.68 ng/mL or TSH values >5.0 μIU/mL or both. Subjects grouped as normal had FT_4 and TSH values within the range >0.68-1.6 ng/mL and 0.4-5.0 μIU/mL, respectively.

Biochemical Investigation

The levels of serum thyroid stimulating hormone (TSH), total triiodothyronine (T_3), free thyroxine (FT_4), and free triiodothyronine (FT_3) were measured by a Microparticle Enzyme Immunoassay (MEIA) on AXSYM System (Abbott Laboratories, Abbott Park, USA); while serum total thyroxine (T_4) was measured by the Fluorescence Polarization Immunoassay (FPIA) method on AXSYM System using the standard laboratory methodologies. Blood glucose, HbA1C, lipids, urea, creatinine, proteins, and microalbuminurea were determined using a fully automated clinical chemistry analyzer (Hitachi 912, Boehringer Mannheim, Germany).

Statistical Analysis

All data were expressed as mean ± SD of the number of experiments. The statistical significance was evaluated by Student's t-test using SPSS version 10.0 (SPSS, Cary, NC USA).

Results

Information about the demographic characteristics of the study population is shown in Table 1. The mean age of diabetic patients was 52 ± 9 and that of control subjects was 47 ± 7. The body mass index of diabetic patients (39 ± 6.2 kg/m^2) was significantly increased compared with that of control subjects (32 ± 5.9 kg/m^2).

Table 1. Demographic characteristics of non-diabetic and diabetic subjects.

STUDY GROUP

Parameter	Non-diabetic subjects	Diabetic patients
Age (years)	47 ± 7	52 ± 9*
Sex-Males	50%	50%
Females	50%	50%
Smokers	15%	20%
Alcohols	12%	17%
Hypertension	12%	25%
Diabetes mellitus	0%	100%
Body mass index (kg/m^2)	32 ± 5.9	39 ± 6.2**

Values are given as mean ± SD from 100 subjects in each group.

Diabetic patients compared with non-diabetic subjects $^*p<0.05$, $^{**}p<0.01$.

Table 2 shows the levels of various biochemical parameters in diabetic and non-diabetic subjects. Blood glucose fasting and postprandial, HbA1C, serum triglyceride, VLDL-C, urea, and microalbuminurea were significantly increased while the levels of total protein, albumin, and HDL-C were significantly decreased in diabetic patients when compared with non-diabetic subjects. Total cholesterol, LDL-C, and creatinine in diabetic and non-diabetic subjects did not differ significantly. Table 3 illustrates the levels of serum thyroid hormones in diabetic and non-diabetic subjects. The level of TSH was significantly decreased whereas the levels of T_4 and FT_4 were significantly increased in diabetic patients compared to control subjects. However, the levels of T_3 and FT_3 in diabetic and non-diabetic subjects did not differ significantly.

Table 2. Comparison of biochemical changes in non-diabetic and diabetic subjects.

STUDY GROUP

Parameter	Non-diabetic subjects	Diabetic patients
Blood glucose		
Fasting (mg/dl)	92 ± 13	195 ± 37***
Postprandial (mg/dl)	125 ± 25	373 ± 30***
HbA1C (%)	3.2 ± 1.7	11.3 ± 2.01***
Microalbuminurea (mg/l)	9 ± 7	42 ± 20***
Urea (mg/dl)	21 ± 15	30 ± 20*
Creatnine (mg/dl)	0.6 ± 0.3	0.7 ± 0.4 NS
Total cholesterol (mg/dl)	165 ± 15	164 ± 17 NS
Triglyceride (mg/dl)	120 ± 30	165 ± 40**
HDL-C (mg/dl)	45 ± 7	37 ± 12*
LDL-C (mg/dl)	75 ± 15	79 ± 20 NS
VLDL-C (mg/dl)	32 ± 10	42 ± 17*
Total protein (g/dl)	7.5 ± 0.6	6.8 ± 1.7*
Albumin (g/dl)	4.1 ± 1.2	3.3 ± 1.5 *

Values are given as mean ± SD from 100 subjects in each group.

Diabetic patients compared with non-diabetic subjects $^*p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, NS (not significant).

Table 4 shows the distribution of diabetics with high, low, and euthyroid thyroid hormone levels. Out of 100 diabetic subjects studied, 28% had low thyroid hormone, 17% had high thyroid hormone, and 55% had euthyroid hormone levels. The incidence of low hormone levels was higher in females (19%) than in males (9%), while the number with high hormone levels was higher in males (10%) than in females (7%).

Discussion

India has the dubious distinction of being home to the largest number of people suffering from diabetes in any country. In theory, treating diabetes should be simple: just prevent hyperglycemia from causing damage to organs and not allow hypoglycemia to cause coma. In practice, it does not work that way. Glucose fluctuations occur all the time. One way to assess the mean levels is to monitor the HbA1c, which gives the average blood glucose level of the preceding 2-3 months. In uncontrolled or poorly controlled diabetes there is an increased glycosylation of a number of proteins, including hemoglobin and a-crystalline of the lenses. HbA1C was found to increase in patients with diabetes to approximately 16%, and the amount of increase was directly proportional to the fasting blood glucose level. During diabetes, the excess glucose present in blood reacts with hemoglobin.[11][12] In the present study, we noticed a marked increase in HbA1C levels in diabetic patients, which could be due to excessive glycosylation of hemoglobin. Diabetes is also grossly reflected by profound changes in protein metabolism and by a negative nitrogen balance and loss of nitrogen from most organs. Increased blood urea production in diabetes may be accounted for by enhanced catabolism of both liver and plasma proteins.[13] Diabetic hyperglycemia induces elevation of the plasma levels of urea and creatinine, which are considered significant markers of renal dysfunction. The decrease in total protein and albumin may be due to microproteinuria and albuminuria, which are important clinical markers of diabetic nephropathy and may be due to increased protein catabolism.

Diabetes has been shown to be associated with numerous thrombotic, atherosclerotic, and cardiovascular diseases. Cholesterol has been singled out as the cause of atherosclerosis. However, other lipids, such as triglycerides and phospholipids, also show similar correlations.[14][15][16] In our study, the levels of serum lipids were found to be elevated in diabetic patients. The abnormally high concentration of serum lipids in diabetes is mainly a result of the increase in mobilization of free fatty acids from peripheral depots. This happens because reduced insulin levels increase the activity of the hormone-sensitive lipase. On the other hand, glucagons, catecholamines, and other hormones enhance lipolysis. The marked hyperlipemia that characterizes the diabetic state may therefore be regarded as a consequence of the uninhibited actions of lipolytic hormones on fat depots.[17] The increase and fall in the individual lipoprotein levels is a reflection of the total serum cholesterol levels; that is, the levels of VLDL-C, LDL-C, and HDL-C increase or decrease with the level of total serum cholesterol, and it is their ratio that determines the pathophysiology of lipoprotein metabolism.[15][18]

Table 3. Serum thyroid hormone levels in non-diabetic and diabetic subjects.

	STUDY GROUP	
Parameter	**Non-diabetic subjects**	**Diabetic patients**
TSH (mIU/ml)	2.44 ± 1.23	1.98 ± 1.01*
T_4 (µg/dl)	8.21 ± 2.10	10.56 ± 4.76**
T_3 (ng/ml)	0.95 ± 0.35	1.00 ± 0.58 NS
FT_4 (ng/ml)	0.26 ± 0.71	1.68 ± 0.85*
FT_3 (pg/ml)	2.87 ± 0.85	3.00 ± 0.75 NS

Values are given as mean ± SD from 100 subjects in each group.

Diabetic patients compared with non-diabetic subjects *$p<0.05$, **$p<0.01$, NS (not significant).

As Johnson et al. said, "The thyroid hormones, triiodothyronine and tetraiodothyronine, are insulin antagonists that also potentiate the action of insulin indirectly."[19] TRH synthesis decreases in diabetes, and this could be responsible for the occurrence of low thyroid hormone levels in diabetics.[20] In our study, the TSH was significantly lower in diabetics than in non-diabetics (1.98 ± 1.01 µIU/mL vs 2.44 ± 1.23 µIU/mL, $p<0.05$). Among the 100 diabetic subjects investigated, 28% had low levels of thyroid hormone while 17% had high levels. All the non-diabetic subjects had euthyroid levels except for one male subject who had a high level. These findings show a high incidence of abnormal thyroid hormone levels (both low and high) in the diabetic population. Our observation is in agreement with the reports of Suzuki et al.[20] and Smithson,[21] who in separate studies found altered thyroid hormone levels of different magnitudes in diabetic patients. The abnormal thyroid hormone levels may be the outcome of the various medications the diabetics were receiving. For example, it is known that insulin, an anabolic hormone, enhances the levels of FT_4 while it suppresses the levels of T_3 by inhibiting hepatic conversion of T_4 to T_3. On the other hand, some of the oral hypoglycemic agents such as the phenylthioureas are known to suppress the levels of FT_4 and T_4, while raising the levels of TSH.[19] Some of the type 2 diabetics were on oral hypoglycemic agents alone and some were on both insulin injections and oral hypoglycemic agents. The type 1 subjects were treated with insulin injections.

Table 4. The distribution of subjects with high, low, or euthyroid thyroid hormone levels.

	STUDY GROUP					
	Non-diabetic subjects			**Diabetic patients**		
	Total	Male	Female	Total	Male	Female
Total	100%	50%	50%	100%	50%	50%
Low level	00%	00%	00%	28%	9%	19%
High level	1%	1%	00%	17%	10%	7%
Euthyroid level	99%	49%	50%	55%	31%	24%

These factors may explain the findings of low or high thyroid hormone levels in diabetic subjects. Nevertheless, the diabetics in our study do not seem to follow the pattern previously recorded in other non-thyroidal diseases such as liver diseases and Cushing's syndrome where low thyroid hormone levels were recorded.[22] The presence of both high and low levels of thyroid hormones in diabetics in this study may also be due to modified TRH synthesis and release and may depend on the glycemic status of the diabetics studied. Glycemic status is influenced by insulin, which is known to modulate TRH and TSH levels.[23]

The TSH level in diabetic males was significantly lower than the level in females (1.68 ± 0.97 µIU/mL vs 2.10 ± 1.05 µIU/mL, $p<0.05$). The incidence of hyperthyroidism was lower in females than in males, but the number of subjects in a hypothyroid state was higher in females than in males. This finding is probably associated with the higher prevalence of obesity recorded in female diabetics. Insulin, which is used in treating diabetes and is produced in normal quantities or in excess, has been associated with increased anabolic activity.[24] Recently, C-peptide has also been shown to enhance Na^+/K^+-ATPase activity, an action that may also increase protein synthesis. Such an action would induce increased turnover of TSH, a protein hormone.[9]

The bulk of the hormones secreted by follicular cells of the thyroid gland are released in the free form into plasma where they become largely bound to thyroid binding globulin (TBG) and to some extent to pre-albumin and albumin. A small fraction circulates free in plasma (FT_4 and FT_3). Suzuki et al.[20] attributed the abnormal thyroid hormone levels found in diabetes to the presence of thyroid hormone binding inhibitor (THBI), an inhibitor of the extrathyroidal conversion enzyme (5'-deiodinase) of T_4 to T_3, and dysfunction of the hypothalamo-pituitary-thyroid axis. These situations may prevail in diabetes and would be aggravated in poorly controlled diabetics. Stress, which is associated with diabetes, may also cause changes in the hypothalamus-anterior pituitary axis in these diabetics. It appears that the presence of subclinical hypothyroidism and hyperthyroidism may result from hypothalamus-hypophyseal-thyroid axis disorders as suggested by Celani et al.[25] Failure to recognize the presence of abnormal thyroid hormone levels in diabetes may be a primary cause of poor management often encountered in some treated diabetics. There is therefore need for the routine assay of thyroid hormones in diabetics, particularly in those patients whose conditions are difficult to manage.

This study has shown a high incidence of abnormal thyroid hormone levels among diabetic patients. In conclusion, our findings demonstrate that detection of abnormal thyroid hormone levels in addition to other biochemical variables in the early stage of diabetes will help patients improve their health and reduce their morbidity rate.

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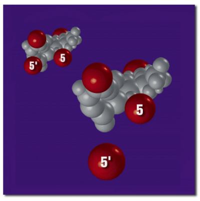

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Thyroid Hormone Changes in Pregnant and Non-Pregnant Women: A Case-Control Study

(Full Text Free in pdf format)

P.Pasupathi,1* V. Chandrasekar,2 and U. Senthil Kumar,3

1Department of Clinical Biochemistry,
2Department of Microbiology,
3Department of Laboratory Medicine,
Bio Line Research Institute,
Coimbatore-641 014, Tamil Nadu, India

**Corresponding author:* Dr. P. Pasupathi, Ph.D.,
Head-Department of Clinical Biochemistry,
Bio Line Research Institute, Coimbatore-641 014 Tamil Nadu, India
Tel: +91 422 4270509 Fax: +91 422 4520099 drppasupathi@gmail.com

ABSTRACT. Pregnancy is associated with significant but reversible changes in thyroid function tests results, which are among the most profound seen as a result of a normal physiologic state. The present study was carried out to find out alterations in thyroid function tests in each trimester in normal pregnant women as compared to non-pregnant women. **Methods:** A case-control study designed with two groups of women: (1) 75 normal pregnant women randomly selected from the first (25 samples), the second (25 samples), and the third (25 samples) trimesters, and (2) 75 randomly selected non-pregnant healthy female controls. Thyroid function tests were carried out by measuring the serum levels of thyroid stimulating hormone (TSH), free and total thyroxin (FT4, T4), and free and total triiodothyronine (FT3, T3) by commercially available radio-immunoassay kits. **Results:** We found that mean T4 increased progressively during pregnancy. Serum levels of T3 increased in the second trimester and then declined during the third trimester compared with non-pregnant women. We also found that FT4 strongly decreased during the third trimester. Free T3 declined in the second and third trimesters. The mean TSH did not significantly differ in the three trimesters compared to the levels of non-pregnant women. **Conclusion:** Thyroid function tests in pregnancy should be interpreted against gestational age-related reference intervals to avoid misinterpretation of thyroid function during pregnancy.

Keywords. FT3 • FT4 • Pregnancy • T3 • T4 • TSH

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Clinical and Laboratory Studies

Evaluation of Serum Lipids and Thyroid Hormone Changes in Non-Pregnant, Pregnant, and Preeclampsia Women

Palanisamy Pasupathi,[1*] Mathiyalagan Deepa.[1]
P. Rani,[2] K.B. Vidhya Sankar,[3] and S.P. Satish kumar[4]

[1]Department of Laboratory Medicine &
[2]Department of Gynecology, Raajam Hospital,
Karruppur, Salem-636 012, Tamil Nadu, India
[3]Department of Radiology & [4]Department of Diabetologe,
Raajam Hospital, Karruppur, Salem-636 012, Tamil Nadu, India

Correspondence: Dr. P. Pasupathi, Ph.D., Head-Department of Laboratory Medicine,
Raajam Hospital, Karruppur Salem-636 012 Tamil Nadu, India
Tel: +91 427 2345145 Mobile: +91 9500476699
Fax: +91 427 2345598 E-mail: drppasupathi@gmail.com

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Abstract. Pregnancy-induced hypertension (PIH) continues to be a major obstetric problem in present-day healthcare practice. To supply adequate nutrition to the growing fetus, maternal physiological adjustments of different organ systems occur in pregnancy. The adjustments include circulatory, metabolic, and hormonal changes. **Objective of Study:** The object of this study was to investigate lipids and thyroid hormone (TT_3, TT_4, FT_3, FT_4 and TSH) status among women who were healthy and non-pregnant (HNP n = 30) compared with health pregnant women (HP n = 30), and pregnant women with preeclampsia (PIH n = 30). **Results:** The mean serum TT_4 and TT_3 in normally pregnant woman were significantly higher compared to the levels in non-pregnant women. However, the mean FT_4 and FT_3 were similar in both normally pregnant and non-pregnant women. In women with preeclampsia, the mean serum TT_4 and TT_3 were significantly higher than in non-pregnant women. But compared to normally pregnant women, women with preeclampsia had a non-significantly higher TT_4 level and a significantly lower TT_3. Compared to non-pregnant women, TSH levels were significantly higher in both preeclamptic and normally pregnant women ($p < 0.001$). In women with preeclampsia, the mean serum FT_4 was not significantly higher than in normally pregnant women, but was significantly higher than in non-pregnant women. The mean serum FT_3 was similar in both non-pregnant and normally pregnant women, but was significantly lower in preeclampsia than in normally pregnant women. **Conclusions:** These findings indicate that there is a state of hypothyroxinemia in normal pregnancy and in preeclampsia, and that biochemical hypothyroidism (raised TSH) occurs. Identifying changes in thyroid hormone status in preeclampsia might be of help in preventing the occurrence of preeclampsia.

Keywords. Lipids • Preeclampsia • Pregnancy • Pregnancy-induced hypertension • T_3 • T_4 • TSH

Introduction

Pregnancy-induced hypertension continues to be a major obstetric problem in present-day healthcare practice. It presents a great medical dilemma because it affects not only maternal health but also puts foetal development at risk. Worldwide, the hypertensive disorders of pregnancy are common and are responsible for 12% of maternal mortality during pregnancy and the puerperium. Preeclampsia is the leading cause of maternal mortality in developed countries and is associated with a five-fold increase in perinatal mortality. The major cause of foetal compromise in preeclampsia is reduced uteroplacental perfusion.[1,2]

Pregnancy is a physiological process. To supply adequate nutrition to the growing fetus, maternal physiological adjustments of different organ systems occur in pregnancy. The adjustments are circulatory, metabolic, and hormonal.[5] Pregnancy is usually associated with mild hyperthyroxinemia, but preeclamptic women have a high incidence of hypothyroidism that might correlate with the severity of preeclampsia.[3,4] On the other hand, preeclampsia has also been observed in 16.7% of cases of subclinical hypothyroidism and 43.7% of cases of overt hypothyroidism during pregnancy.[5]

Table 1. Shows the demographic characteristics of study population in non-pregnant, pregnant and preeclepsia subjects.

Parameter	**Non-pregnant Women**	**Healthy Pregnant Women**	**Preeclampsia Women**
Total number of subjects (n)	30[100%]	30{100%]	30 [100%]
Mean age (mean ± SD; years)	25 ± 5	28 ± 9	27 ± 8
Weight	55 ± 8	65 ± 5	67 ± 7
Body mass index (Kg/m2)	23 ± 3.0	27 ± 4.6**	29 ± 5.3$^{¤¤¤}$
Hypertension	-	-	30 [100 %]
Average Systolic blood pressure (mm of Hg)	120 ± 2	119 ± 2^{NS}	167 ± 20$^{¤¤¤‡}$
Average Diastolic blood pressure (mm of Hg)	80 ± 1	80 ± 2^{NS}	117 ± 12$^{¤¤¤‡}$
Average period of gestation	-	36 weeks	35 weeks

Values are given as mean ± S.D from 30 subjects in each group.
¤ Preeclampsia women compared with non-pregnant women ($^{¤¤¤}p < 0.001$)
* Normal pregnant women compared with non-pregnant women (**$p < 0.01$, ^{NS}-Not significant)
‡ Preeclampsia women compared with normal pregnant women ($^{‡}p < 0.001$)

Dyslipidemia is common in preeclampsia, and, via oxidation of susceptible lipids, may contribute to endothelial activation. We previously reported that triglyceride and free fatty acids were elevated as early as in the first and second trimesters in women who subsequently developed preeclampsia. Hyperlipidemia in preeclampsia is associated with a predominance of both atherogenic small low-density lipoproteins (LDL) and vascular cell adhesion molecutes.[6,7]

In preeclampsia, the most affected organs are liver, kidneys, and brain. Due to autointoxication, functional disorders in these organ systems are evident.[8] As liver, kidneys, and muscles are the main organs of peripheral deiodination of T_4 to T_3, the serum concentration of T_4 and T_3 may different in preeclampsia than in normal pregnancy.[5] In India, where preeclampsia/eclampsia is among major health problems, little research of the conditions has yet been done. The present study examines the lipids and thyroid hormonal levels in healthy pregnant women, those with preeclampsia, and healthy non-pregnant (control) subjects.

Materials and Methods

Study Population. The study population we investigated consisted of 90 women divided into three groups. Ages ranged from 19-to-37 years. The three groups consisted of 30 healthy non-pregnant women, 30 normally healthy pregnant women, and 30 pregnant women with preeclampsia.

The prospective study was carried out at the Raajam Hospital, Karruppur, Salem, Tamil Nadu, India, between January 2008 to January 2009. The study was approved by the Human Bioethics Committee for Clinical Research of the Raajam Hospital. Informed verbal consent was obtained from all subjects.

The objectives of the study were explained and a written concept was taken from each subject. Detailed case histories were obtained and bedside urine examination for sugar was done. Women who gave a present or past history of thyroid disease, diabetes mellitus, or glycosuria were excluded from the study.

Classification of the values into raised, low, or normal thyroid hormone levels were based on the following criteria: Subjects classified as having raised levels of thyroid hormone had FT$_4$ values > 1.6 ng/L, TSH levels < 0.4 miu/mL, or both. Subjects classified as having low FT$_4$ values had < 0.68 ng/mL, TSH values > 5.0 miu/mL, or both. Subjects grouped as normal had FT$_4$ and TSH values within the range of > 0.68–1.6 ng/mL and 0.4–5.0 miu/mL, respectively.

Table 2. Lipids level changes in non-pregnant, pregnant, nd preeclempsia subjects.

Parameter	Non-pregnant Women	Normal Pregnant Women	Preeclampsia Women
Total cholesterol (mg/ dl)	154 ± 12.7	168 ± 10.5^{NS}	221 ± 18.8$^{¤¤¤‡}$
Triglyceride (mg/dl)	92 ± 11.5	132 ± 18**	252 ± 22$^{¤¤¤‡}$
HDL-cholesterol (mg /dl)	47 ± 4	44 ± 5^{NS}	34 ± 7$^{¤¤‡}$
LDL-cholesterol (mg /dl)	78 ± 8	85 ± 10^{NS}	138 ± 13$^{¤¤¤‡}$
VLDL-cholesterol (mg /dl)	25 ± 5	39 ± 6*	50 ± 5$^{¤¤‡}$

Values are given as mean ± S.D from 30 subjects in each group.
¤Preeclampsia women compared with non-pregnant women (¤¤*p* <0.01, ¤¤¤*p* < 0.001)
*Normal pregnant women compared with non-pregnant women (**p* < 0.05, ***p* < 0.01, ^{NS}-Not significant)

Sample collection. Single samples of 10-ml of ante-cubical venous blood was obtained with aseptic measure. After let to clot, the blood was centrifuged for 30 minutes and the supernatant (serum) was taken in a separate test tube. Thus, the serum was ready and used for hormone analysis in the laboratory.

Biochemical Investigation. The levels of serum thyroid stimulating hormone (TSH), total triiodothyroxine (T$_3$), free thyroxine (FT$_4$), and free triiodothyronine (FT$_3$) were measured by a Microparticle Enzyme Immunoassay (MEIA) on the AXSYM System (Abbott Laboratories, Abbott Park, USA). Serum total thyroxine (TT$_4$) was measured by the Fluorescence Polarization Immunoassay (FPIA) method on AXSYM System using standard laboratory methodologies. Serum lipids were determined using a fully automated clinical chemistry analyzer (Hitachi 912, Boehringer Mannheim, Germany).

Statistical Analysis. All data were expressed as mean ± S.D of number of experiments. The statistical significance was evaluated by Student's *t*-test using SPSS version 10.0 (SPSS, Cary, NC, USA).

Results

Table 1 shows the demographic characteristics of the study population in non-pregnant, pregnant, and preeclampsia subjects. All the studied groups had a similar mean age and mean pregnancy period. Indices of obesity (weight and BMI) were significantly increased in the pregnancy groups compared to the control group of non-pregnant women. Mean blood pressure (both systolic and diastolic) and urine protein were significantly raised in preeclamptic patients compare with pregnant and non-pregnant subjects.

Table 2 shows the lipid level changes in non-pregnant, pregnant, and preeclempsia subjects. The lipid profile (total cholesterol, triglyceride, VLDL, and LDL-C) levels were significantly higher in the preeclamptic patients compare to healthy pregnant and non-pregnant subjects. The mean plasma HDL-C concentration, however, was much lower in preeclamtic subjects than in the other groups of women. The mean lipid levels, therefore, were statistically significantly different in preeclampsia women than in normal pregnant women.

Table 3. Showing mean ± SE of TT_3, TT_4, FT_3, FT_4 and TSH in non-pregnant,pregnant and preeclempsia subjects.

Parameter	Non-pregnant Women	Normal Pregnant Women	Preeclampsia Women
TT_3 (ng/ml)	0.87 ± 0.19	2.17 ± 0.57*	1.85 ± 0.49$^{\ddagger ¤}$
TT_4 (µg/dl)	7.01 ± 2.32	12.62 ± 5.16*	12.75 ± 5.08$^{\ddagger NS}$
FT_3 (pg/ml)	2.65 ± 0.79	3.57 ± 1.21*	2.72 ± 1.15$^{\ddagger ¤¤}$
FT_4 (ng/ml)	1.15 ± 0.52	2.38 ± 0.99*	2.42 ± 0.75$^{\ddagger NS}$
TSH (mIU/ml)	2.15 ± 1.23	3.89 ± 2.32*	5.24 ± 2.58$^{\ddagger ¤¤¤}$

Values are given as mean ± S.D from 30 subjects in each group.
Normal pregnant women compared with non-pregnant women ($p < 0.001$)
‡Preeclampsia women compared with Non-pregnant women ($^{\ddagger}p < 0.001$)
$^{¤}$Preeclampsia women compared with Normal pregnant women
($^{¤}p < 0.05$, $^{¤¤}p < 0.01$, $^{¤¤¤}p < 0.001$, ^{NS}-Not Significant)

Table 3 illustrates the serum thyroid status (TT_3, TT_4, FT_3, FT_4 and TSH) of non-pregnant, pregnant, and preeclempsia subjects. The mean serum TT_4 and TT_3 in normal pregnancy were significantly higher compared to that of non-pregnant women. Mean FT_4 and FT_3 levels were similar in both normal pregnancy and non-pregnant women. In preeclampsia, the mean serum TT_4 and TT_3 levels were significantly higher than in non-pregnant women. But compared to the level of women with normal pregnancies, TT_4 was clearly higher but not significant when TT_3 was significantly lower.

Mean TSH levels were significantly higher in normal pregnant women than in non-pregnant women ($p < 0.001$). But the mean TSH level for preeclampsia woman was even higher than in either other the other two groups, and the mean preeclampsia level was significantly higher than that in normal pregnant women ($p < 0.001$).

The mean serum FT_4 level was significantly higher in preeclampsia compared to non-pregnant women. However, FT_4 levels did not significantly differ between women with normal pregnancies and those with preeclampsia. The mean serum FT_3 was significantly higher in women with normal pregnancies than in non-pregnant women. Subjects with preeclampsia had significantly higher FT_3 than non-pregnant women but a significantly lower mean level than women with normal pregnancies.

Discussion

Our finding in this study of increased mean BMI in both groups of pregnant women could partly explain the significant increase in triglycerides and LDL; increases in weight and BMI are associated with an increase in body fat percentage levels.

It is known that preeclampsia is associated with hypertriglyceridemia. The above-mentioned interactions along with increased endothelial triglyceride accumulation may result in endothelial cell dysfunction during gestation. Increased triglycerides found in the pregnancy-induced hypertension (which we call preeclampsia) is likely to be deposited in predisposed vessels, such as the uterine spiral arteries. If so, this may contribute to endothelial dysfunction, both directly and indirectly, through the generation of small, dense LDL. Moreover, this hypertriglyceridemia may be associated with hypercoagulability.[9,10]

A significant fall in LDL-C concentration in the control group in this present study may be attributed to hyperoestrogenaemia. On the other hand, LDL-C levels increased significantly in the pregnancy-induced hypertension subjects. Moreover, other studies have also demonstrated a predominance of the atherogenic small LDL and that vascular cell adhesion molecules are increased in association with hyperlipidemia in preeclampsia. The endothelial dysfunction in preeclampsia could originate from oxidative stress as well as dyslipidaemia. Many different enzymatic processes can generate free radicals. They are extremely reactive and interact with polyunsaturated fatty acids to produce lipid peroxides with a much longer half-life.[11,12]

In the present study, we evaluated thyroid status in normal pregnancy and preeclampsia without detectable thyroid abnormalities. Elevation in serum thyroid hormone levels in pregnancy indicates an important modification of thyroid activity in pregnancy.[8]

In this study, serum TT_4 and TT_3 were significantly higher in pregnant woman compared to non-pregnant control, whereas free forms of the hormones (FT_4 and FT_3) were similar in both groups. The increase in serum binding forms of thyroid hormone may be due to the marked increase in the circulating level of the major T_4 binding protein, thyroid-blinding globulin. This globulin is induced by high estrogen levels in pregnancy. In addition, in pregnancy, the stimulatory effect of serum hCG of placental origin, increased metabolic demand, and mental stress may play increase overall thyroid activity and elevate thyroid hormone levels.

During pregnancy, increased estrogen levels cause increased production of proteins by the liver. As a result, hypatocytes increases their production of thyroid-binding globulin, the protein that tranaports T_4 in the circulation. High estrogen, on the other hand, due to oligosaccharide modification, reduces peripheral degradation of thyroid-binding globulin. As a result, the content of thyroid-binding globulin in the serum is increased. As the binding capacity of the plasma is increased due to the elevated serum level of thyroid-binding globulin, more hormones bind to the globulin. As a result, the total plasma content of thyroid hormones is increased. Despite this, free thyroid hormone levels remain unchanged and hyperthyroidism does not occur.

Different studies are controversial regarding free hormone levels during pregnancy. Different investigators have found that free hormone levels remain unchanged, decrease, or even increase in pregnant women compared to non-pregnant controls. The present study shows no significant change in free thyroid hormone levels between non-pregnant and pregnant women; the study, then, contributes to the ongoing controversy.[13]

In this study, we also compared thyroid hormone levels in preeclampsia to those in normal pregnancy. In preeclampsia, the mean serum total and free T_4 levels were slightly higher than in women with normal pregnancies but the levels of the two groups did not reach statistical significance. However, compared to women with normal pregnancies, women with preeclampsia did have statistically significantly lower total and free T_3 levels. We believe that reduced extrathyroidal conversion of T_4 to T_3 was the cause of the non-significant higher T_4 levels and significant lower T_3 levels in preeclampsia.

Preeclampsia is pregnancy-induced autointoxication with multisystem disorders; the most affected organs are brain, liver, and kidneys. Functional disorders in these organ systems are evident in preeclampsia.[14]

However, the liver and kidneys are the most important organs in peripheral deiodination (conversion of T_4 to T_3) and in the maintenance of normal blood levels of T_4 and T_3. This is why involvement of liver and kidneys in preeclampsia is likely to change serum T_4 and T_3 levels.

In some other studies, investigators have observed that preeclamptic women may affected by a variety of conditions. These include systemic illnesses, protein-energy malnutrition, starvation, anorexia nervosa, Cushing's syndrome, and excessive steroid therapy. When the women have developed such systemic disorders, the extrathyroidal deiodination of T_4 to T_3 has been reduced.[15] Due to wide range of normal limits, however, the differences in T_4 and T_3 usually neither exceed normal limits nor produce significant metabolic changes.

Conclusion. The main finding of the current study is a statistically significantly higher number of cases pregnant women with preeclampsia who had abnormally high TSH levels. Thyroid gland diseases are predisposing factors for the development of preeclampsia. If the titers of TSH are above 5 mIU/ml, then the risk of developing preeclampsia is 4.8 times higher. This high-risk potential marker of preeclampsia needs further investigation because of the small number of subjects in this study. A multicenter study may reveal the association and mechanism of thyroid abnormalities in preeclamptic women in different geographical regions. Such a study, by enabling us to identify thyroid abnormalities and take appropriate therapeutic action to correct them, might lower the occurrence and severity of morbidity and mortality associated with preeclampsia.

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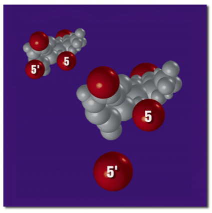

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Free Radical Activity and Antioxidant Defense Mechanisms in Patients with Hypothyroidism

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Palanisamy Pasupathi* **and Raman Latha****

*Institute of Laboratory Medicine, K.G. Hospital and Post Graduate Medical Institute,
Coimbatore-641 018, Tamil Nadu, India
**Department of Diabetic Medicine, K.G. Hospital and Post Graduate Medical Institute,
Coimbatore-641 018, Tamil Nadu, India

Contact: Dr. P. Pasupathi, PhD drppasupathi@gmail.com

ABSTRACT. Free radical-mediated oxidative stress has been implicated in the etiopathogenesis of several autoimmune disorders. Hypothyroidism in humans is widely believed to impair health. The biochemical factors mediating decline in health, however, are poorly elucidated. Pathological consequences of hypothyroidism point to a high potential for antioxidant imbalance. The study population consisted of 60 subjects divided into two groups: 30 people with hypothyroidism and 30 age-matched healthy participants. We examined the levels of total triiodothyronine (T3), free triiodothyronine (FT3), total thyroxine (T4), free thyroxine (FT4), thyroid stimulating hormone (TSH), thiobarbituric acid reactive substances (TBARS), and enzymatic and non-enzymatic antioxidant status. The mean TSH level was significantly higher in hypothyroid patients than in control subjects. On the other hand, the levels of FT4, T4, FT3, and T3 were significantly lower in hypothyroid patients compared to control subjects. The mean level of plasma thiobarbituric acid reactive substances (TBARS) was significantly higher in hypothyroid patients than in healthy controls. However, the activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-S-transferase (GST), and reduced glutathione (GSH) were significantly lower in hypothyroid patients than in control subjects. Our preliminary results confirm the hypothesis that people with hypothyroidism have reduced antioxidative defense.

Keywords. Antioxidant status • Hypothyroidism • Lipid peroxidation • Oxidative stress

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Palanisamy Pasupathi* and Raman Latha**

*Institute of Laboratory Medicine, K.G. Hospital and Post Graduate Medical Institute,
Coimbatore-641 018, Tamil Nadu, India
**Department of Diabetic Medicine, K.G. Hospital and Post Graduate Medical Institute,
Coimbatore-641 018, Tamil Nadu, India

Contact: Dr. P. Pasupathi, PhD drppasupathi@gmail.com

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Abstract. Free radical-mediated oxidative stress has been implicated in the etiopathogenesis of several autoimmune disorders. Hypothyroidism in humans is widely believed to impair health. The biochemical factors mediating decline in health, however, are poorly elucidated. Pathological consequences of hypothyroidism point to a high potential for antioxidant imbalance. The study population consisted of 60 subjects divided into two groups: 30 people with hypothyroidism and 30 age-matched healthy participants. We examined the levels of total triiodothyronine (T_3), free triiodothyronine (FT_3), total thyroxine (T_4), free thyroxine (FT_4), thyroid stimulating hormone (TSH), thiobarbituric acid reactive substances (TBARS), and enzymatic and non-enzymatic antioxidant status. The mean TSH level was significantly higher in hypothyroid patients than in control subjects. On the other hand, the levels of FT_4, T_4, FT_3, and T_3 were significantly lower in hypothyroid patients compared to control subjects. The mean level of plasma thiobarbituric acid reactive substances (TBARS) was significantly higher in hypothyroid patients than in healthy controls. However, the activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione-S-transferase (GST), and reduced glutathione (GSH) were significantly lower in hypothyroid patients than in control subjects. Our preliminary results confirm the hypothesis that people with hypothyroidism have reduced antioxidative defense.

Keywords. Antioxidant status • Hypothyroidism • Lipid peroxidation • Oxidative stress

Introduction

Thyroid hormones are among the most important humoral factors involved in setting the basal metabolic rate on a long-term basis in target tissues such as liver, heart, kidney and brain.[1] Oxygen free radicals can develop during several steps of normal metabolic events. Although free radicals have the potential to damage the organism, their generation is inevitable for some metabolic processes. The main endogenous sources of free radicals are the mitochondrial electron transport chain, the microsomal membrane electron transport chain, reactions of oxidant enzymes, and auto-oxidation reactions.[2][3][4]

Both hydrogen peroxide and superoxide anion produce highly reactive hydroxyl radicals through the Haber-Weiss reaction. The hydroxyl radical can initiate lipid peroxidation, which is a free radical chain reaction leading to damage of membrane structure and function.[5] Variations in the levels of thyroid hormones can be one of the main physiological modulators of *in vivo* cellular oxidative stress due to their known effects on mitochondrial respiration. In particular, it has been suggested that the increase in reactive oxygen species induced by a deficiency of thyroid hormones can lead to an oxidative stress condition in the liver and in the heart and some skeletal muscles with a consequent lipid peroxidative response.[4]

Reactive oxygen species (ROS) including partially reduced forms of oxygen; i.e. superoxide anion, hydrogen peroxide, and hydroxyl radical, as well as organic counterparts such as lipid peroxides; are produced as natural consequences of oxidative cell metabolism.[6] Under physiological conditions, ROS generation is controlled by a large number of anti-free radical systems which act as protective mechanisms. These systems consist of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase as well as non-enzymatic antioxidants, among which the most important are vitamins C and E, carotenoids, and glutathione. Disturbance of the prooxidant/antioxidant balance results from the increased production of ROS, inactivation of detoxification systems, or excessive consumption of antioxidants. The disturbance is a causative factor in the oxidative damage of cellular structures and molecules such as lipids, proteins, and nucleic acids.[7]

Subclinical hypothyroidism is defined as a serum thyroid stimulating hormone (TSH) concentration above the statistically defined upper limit of the reference range when serum free T_4 concentration is within its reference range. Greater sensitivity of assays and more frequent assessment of serum TSH levels have resulted in more patients requiring interpretation of abnormal thyroid function test results. However, controversy surrounds the definition, clinical importance, and necessity for prompt diagnosis and treatment of hypothyroid disease. Previous review articles and position statements differ in their conclusions and recommendations, often a consequence of difficulties in interpreting inadequate and conflicting data.[8] In the midst of this uncertainty, clinicians still desire expert guidance for the diagnosis and management of hypothyroid disease.

Hypothyroidism-associated oxidative stress is the consequence of both increased production of free radicals and reduced capacity of the antioxidative defense.[9][10] Hypothyroidism-induced dysfunction of the respiratory chain in the mitochondria leads to accelerated production of free radicals (i.e., superoxide anion, hydrogen peroxide, and hydroxyl radical as well as lipid peroxides), which consequently leads to oxidative stress (OS).[4][11] Metabolic disorder from autoimmune-based hypothyroidism can also increase oxidative stress.[13]

Methods

Study Population

The study population consisted of 60 subjects (age- and sex-matched) divided into two groups: hypothyroid patients (n=30) and healthy control subjects (n=30). All the patients and controls were recruited from K.G. Hospital and Post Graduate Medical Institute, Coimbatore, Tamil Nadu, India, during January of 2007-to-March of 2008. General health characteristics such as age, sex, smoking status, menopausal status, alcohol consumption, and dietary habits (particularly as related to preference) were investigated by a self-administered questionnaire. We classified values into high, low, or normal thyroid hormone levels by the following criteria. Subjects classified as having a high level of thyroid hormones had FT_4 values > 1.6 ng/mL or TSH < 0.4 µIU/mL, or both. Those classified as having a low level had FT_4 values < 0.68 ng/mL or TSH values > 5.0 µIU/mL, or both. Subjects grouped as normal had FT_4 and TSH values within the reference ranges > 0.68-to-1.6 ng/mL and 0.4-to-5.0 µIU/mL, respectively.

Blood Collection and Hemolysate Preparation

Blood samples were collected by venous puncture in heparinized tubes and the plasma was separated by centrifugation at 1000 g for 15 minutes After centrifugation, the buffy coat was removed and the packed cells were washed three times with physiological saline. A known volume of the erythrocytes was lysed with hypotonic phosphate buffer (pH 7.4). The hemolysate was separated by centrifugation at 2500 g for 15 minutes at 2°C.

Biochemical Investigation

The level of serum lipids was determined using a fully automated clinical chemistry analyzer (Hitachi 912, Boehringer Mannheim, Germany). The levels of serum thyroid stimulating hormone (TSH), total triiodothyronine (T_3), free thyroxine (FT_4), and free triiodothyronine (FT_3) were measured by a Microparticle Enzyme Immunoassay (MEIA) on the AXSYM System (Abbott Laboratories, Abbott Park, USA), while the serum total thyroxine (T_4) was measured by the Fluorescence Polarization Immunoassay (FPIA) method on the AXSYM System using the standard laboratory methodologies.

Estimation of Lipid Peroxidation

Lipid peroxides were estimated by measurement of thiobarbituric acid reactive substances in plasma by the method of Yagi.[14] The pink chromogen produced by the reaction of thiobarbituric acid with malondialdehyde (a secondary product of lipid peroxidation) was estimated. The absorbance of clear supernatant was measured against reference blank at 535 nm.

Assay of Superoxide Dismutase and Catalase

Superoxide dismutase (SOD) was assayed using the technique of Kakkar et al.[15] based on inhibition of the formation of nicotinamide adenine dinucleotide, phenazine methosulfate, and amino blue tetrazolium formazan. A single unit of enzyme was expressed as 50% inhibition of NBT (Nitroblue tetrazolium) reduction min/mg/Hb. Catalase (CAT) was assayed colorimetrically at 620 nm and expressed as μmole of H_2O_2 consumed min/mg/Hb as described by Sinha.[16] The reaction mixture (1.5 mL) contained 1.0 mL of 0.01 mole pH 7.0-phosphate buffer, 0.1 mL of hemolysate, and 0.4 mL of 2 mole H_2O_2. The reaction was stopped by the addition of 2.0 mL of dichromate-acetic acid reagent (5% potassium dichromate and glacial acetic acid were mixed in 1:3 ratio).

Estimation of Reduced Glutathione

Reduced glutathione (GSH) content was determined by the method of Ellman.[17] Plasma,1.0 mL, was treated with 0.5 mL of Ellman's reagent (19.8 mg of 5,5'-dithiobisnitro-benzoic acid [DTNB] in 100 mL of 0.1% sodium nitrate) and 3.0 mL of phosphate buffer (0.2 M, pH 8.0). The absorbance was read at 412 nm.

Assay of Glutathione Peroxidase

Glutathione peroxidase (GPx) activity was measured using the method described by Rotruck et al.[18] with modifications. Briefly, the reaction mixture contained 0.2 mL of 0.4 mole Tris-HCl buffer pH 7.0, 0.1 mL of 10 mmole sodium azide, 0.2 mL of hemolysate, 0.2 mL glutathione, and 0.1 mL of 0.2 mmole hydrogen peroxide. The contents were incubated at 37˚C for 10 minutes. The reaction was arrested by 0.4 mL of 10% TCA, and the contents centrifuged. The supernatant was assayed for glutathione content using Ellman's reagent. GPx activity was expressed as μmole of GSH consumed min/mg/Hb.

Assay of Glutathione-S-transferase

Glutathione-S-transferase (GST) activity was determined spectrophotometrically using the method of Habig et al.[19] The reaction mixture contained 1.0 mL of 0.3 mmole phosphate buffer (pH 6.5), 0.1 mL of 30 mmole 1-chloro-2, 4-dinitrobenzene (CDNB), and 1.7 mL of double distilled water. After preincubating the reaction mixture at 37˚C for 5 minutes, the reaction was started by the addition of 0.1 mL of hemolysate and 0.1 mL of glutathione as substrate. The absorbance was followed for 5 minutes at 340 nm. Reaction mixture without the enzyme was used as blank. The activity of GST is expressed as μmole of CDNB-GSH conjugate formed/min/mg/Hb using an extinction coefficient of 9.6 mmole-1 cm-1.

Statistical Analysis

All data were expressed as mean ± SD of number of experiments. The statistical significance was evaluated by Student's t-test using SPSS version 10.0 (SPSS, Cary, NC, USA).

Results

Demographic characteristics of the study population are shown in Table 1. The mean age of hypothyroid patients was 43±14 years and of control subjects, 47±13 years. Hypothyroid patients had a significantly increased body mass index (31±5.1kg/m^2) compared to control subjects (27±4.5kg/m^2). However, the levels of serum lipids in hypothyroid patients and control subjects did not differ significantly.

Table 1. Demographic characteristics and lipids in control subjects and hypothyroidism.

Parameter	Control subjects	Hypothyroid patients
No. of subjects	30	30
Age (years)	47±13	43±14
Duration of HPO (years)	—	4.9±2.1
Body mass index (kg/m^2)	27±4.5	31±5.1*
Total cholesterol (mg/dl)	187±21	190±19 NS
Triglyceride (mg/dl)	142±23	140±26 NS
HDL-C (mg/dl)	40±9	38±10 NS
LDL-C (mg/dl)	62±11	59±12 NS

Values are given as mean ± SD from 30 subjects in each group.

Hypothyroid patients compared with control subjects: *$p<0.05$; NS=not significant.

Table 2 shows the serum TSH and thyroid hormone levels of hypothyroid patients and control subjects. Compared to control subjects, the hypothyroid patients' mean TSH level was significantly higher.

Hypothyroid patients also had significantly lower levels of T_4, FT_4, FT_3, and T_3.

Table 3 illustrates the level of circulatory lipid peroxidation and antioxidant status in control subjects and hypothyroid patients. The extent of lipid peroxidation TBARS was significantly increased in hypothyroid patients when compared to healthy controls. For studying the deleterious consequence of diabetes on antioxidant status, the activities of the enzymatic antioxidants SOD, CAT, GPx, GST, and the non-enzymatic antioxidant GSH were measured. The activities of the enzymatic antioxidants and the level of GSH were significantly lower in hypothyroid patients when compared to healthy subjects.

Table 2. Serum thyroid hormone status in control subjects and hypothyroidism.

Parameter	Control subjects	Hypothyroid patients
FT_4 (ng/ml)	1.16±0.71	0.53±0.10**
FT_3 (pg/ml)	2.87±0.85	2.21±0.62 *
T_4 (μg/dl)	8.21±2.10	1.86±0.91***
T_3 (ng/ml)	0.95±0.25	0.51±0.11**
TSH (mIU/ml)	2.24±1.17	15.83±4.18***

Values are given as mean ± SD from 30 subjects in each group.

Hypothyroid patients compared with control subjects: *p<0.05, **p<0.01, ***p<0.001.

Discussion

Resch et al.[20] found that hypothyroidism was associated with enhanced oxidative stress and lipid peroxidation, and supposed that this might lead to the development and progression of atherosclerosis. In our study, hypothyroid patients' level of TBARS was higher than that of healthy subjects. Our data showed a significantly decreased SOD activity in hypothyroid patients compared to controls. In addition, the activities of the enzymes GPx and CAT were also clearly significantly lower in patients than in healthy subjects.

ROS have been reported to induce oxidative damage to membrane lipids, proteins, and DNA, and might result in cell death by necrosis or apoptosis.[21] Both GPX and CAT are major defenses against harmful effects of ROS in cells, and in cultured thyrocytes, both have a high capacity to degrade exogenous hydrogen peroxide (H_2O_2).[22] Specifically, observations indicate that GPx is involved in the degradation of fairly low H_2O_2 levels, whereas CAT is required to degrade H_2O_2 at higher concentrations. It is thus possible that the lower activities of GPx and CAT lead to H_2O_2-induced apoptosis of thyroid cells in Hashimoto's thyroiditis patients. In an *in vitro* study by Demelash et al.,[23] impaired capacity of GPx in degrading H_2O_2 in cultured thyroid pig cells aggravated the apoptic response. This data and our results suggest the possibility that reduced GPx and CAT activities in hypothyroid patients might participate in the initiation of the autoimmune process and might lead to H_2O_2-induced damage of thyroid cells related to cytosolic oxidative stress.

The mechanism linking hypothyroidism with oxidative stress and antioxidants is unknown. The effects of hypothyroidism on antioxidant parameters have been investigated in hypothyroid patients with intellectual disability.[4] The study showed that despite good medical care, patients had a decrease in the activity of three antioxidant defenses. Changes were more prominent among male subjects.

Table 3. Circulatory lipid peroxide and antioxidant status in control subjects and hypothyroid patients.

Parameter	Control subjects	Hypothyroid patients
TBARS (nmole/ml)	2.62±0.42	6.32±0.45***
SOD (Unit a mg/Hb)	2.91±0.46	1.83±0.27***
CAT (Unit b mg/Hb)	70.5±10.61	48.5±9.30***
GPx (Unit c mg/Hb)	8.75±2.32	6.21±1.55***
GST (Unit d mg/Hb)	2.52±0.45	1.05±0.40***
GSH (mg/dl)	41.11±7.52	25.36±4.91**

Values are given as mean ± SD from 30 subjects in each group.

Hypothyroid patients compared with control subjects: **p<0.01,***p<0.001.

Unit a- One unit of activity was taken as the enzyme reaction, which gave 50% inhibition of NBT reduction in one minute.

Unit b - μmole of H_2O_2 consumed/minute.

Unit c - μmole of GSH consumed/min.

Unit d - μmole of CDNB–GSH conjugate formed/min.

Antioxidant deficiencies may lead to a failure to effectively combat extrinsic factors (i.e., weather, diet, drugs, and physical exercise) and intrinsic factors (i.e., injuries, weakness, and fatigue) involved in oxidative stress. An extensive body of evidence now exists confirming that antioxidants are involved in the cellular defense against oxidative stress in a variety of pathological conditions. It has been suggested that hypothyroidism leads to oxidative stress and to a reduction of antioxidant defenses. In addition, previous experimental studies have reported that hypothyroidism is characterized by endothelial dysfunction of blood vessels.[24] To determine the status of the antioxidant system in relation to thyroid gland dysfunction, we used a complex of different diagnostic indicators related to damage of various biological tissues.

Although the pathophysiological consequences of the decelerated antioxidant levels are not yet elucidated, this biochemical change is thought to be a physiological adaptation and response to hypothyroidism. In agreement with previous findings, thyroid hormones are involve in combating the toxicity of oxidative stress in animals[25] and in humans.[12] Thus, under normal conditions, the protective effect of thyroid hormone against oxidative stress can be explained by the function of antioxidants as a defense system.

However, a chronic state of hypothyroidism is characterized by impairments in the redox potential. This leads to free radical chain reactions and to metabolic suppression of antioxidant capacity. Our results from this study support the suggestion that the hypothyroidism of patients with intellectual disability in some way is linked to the low levels of the major antioxidant molecules found in these patients. The depletion of antioxidants observed in hypothyroid individuals may reflect the increased free radical production in the electron transport chain in the mitochondrial inner membrane. The increase of free radicals is not compensated, as one would expect, by a decrease of antioxidants. A high oxidative state in hypothyroid people has metabolic and biochemical characteristics such as increased mitochondrial enzyme activity. Thus, it is likely that patients' cells are damaged by prolonged oxidative stress that far exceeds the capacity of the patients' organs to synthesize antioxidant molecules or to synthesize them from extracellular sources.[6]

Hypothyroidism is generally associated with decreased content of tissue protein. Hypothyroidism also specifically reduces most tissues' cellular thiol reserve and alters glutathione/GSH-Px content. Our hypothyroid patients had significantly decreased SOD activity. Importantly, SOD is the first line of enzymatic defense against intracellular free radicals. Because of that, a decrease of SOD activity would expose the cell membrane and other components to oxidative damage. Catalase shares with GSH-Px its function of catalyzing the decomposition of H_2O_2 to water. A low level of catalase activity, then, could primarily damage the endoplasmic reticulum in the cells. Glutathione reductase was little affected by the presence of hypothyroidism.[11]

In conclusion, our present study suggests a very high production of ROS and oxidative stress in patients with hypothyroidism, with enhanced lipid peroxidation and concomitant failure of antioxidant defense mechanisms. Physical signs and symptoms in people with hypothyroidism are less reliable and there is a need for serum testing to determine the appropriate dosage of replacement thyroid hormones. Our purpose in this study was to provide evidence for, and to recommend, blood testing for hypothyroid patients' antioxidant system in order to monitor the progression of pathology and to prompt the consideration of medical care.

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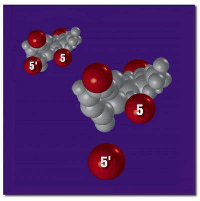

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Thyroid Hormone Changes in Pregnant and Non-Pregnant Women: A Case-Control Study

(Full Text Free in pdf format)

P.Pasupathi,1* V. Chandrasekar,2 and U. Senthil Kumar,3

1Department of Clinical Biochemistry,
2Department of Microbiology,
3Department of Laboratory Medicine,
Bio Line Research Institute,
Coimbatore-641 014, Tamil Nadu, India

**Corresponding author:* Dr. P. Pasupathi, Ph.D.,
Head-Department of Clinical Biochemistry,
Bio Line Research Institute, Coimbatore-641 014 Tamil Nadu, India
Tel: +91 422 4270509 Fax: +91 422 4520099 drppasupathi@gmail.com

ABSTRACT. Pregnancy is associated with significant but reversible changes in thyroid function tests results, which are among the most profound seen as a result of a normal physiologic state. The present study was carried out to find out alterations in thyroid function tests in each trimester in normal pregnant women as compared to non-pregnant women. **Methods:** A case-control study designed with two groups of women: (1) 75 normal pregnant women randomly selected from the first (25 samples), the second (25 samples), and the third (25 samples) trimesters, and (2) 75 randomly selected non-pregnant healthy female controls. Thyroid function tests were carried out by measuring the serum levels of thyroid stimulating hormone (TSH), free and total thyroxin (FT4, T4), and free and total triiodothyronine (FT3, T3) by commercially available radio-immunoassay kits. **Results:** We found that mean T4 increased progressively during pregnancy. Serum levels of T3 increased in the second trimester and then declined during the third trimester compared with non-pregnant women. We also found that FT4 strongly decreased during the third trimester. Free T3 declined in the second and third trimesters. The mean TSH did not significantly differ in the three trimesters compared to the levels of non-pregnant women. **Conclusion:** Thyroid function tests in pregnancy should be interpreted against gestational age-related reference intervals to avoid misinterpretation of thyroid function during pregnancy.

Keywords. FT3 • FT4 • Pregnancy • T3 • T4 • TSH

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Thyroid Hormone Changes in Pregnant and Non-Pregnant Women: A Case-Control Study

P.Pasupathi1,[1*] V. Chandrasekar,[2] and U. Senthil Kumar,[3]

[1]Department of Clinical Biochemistry, Bio Line Research Institute, Coimbatore- 641 014, Tamil Nadu, India
[2]Department of Microbiology, Bio Line Research Institute, Coimbatore-641 014, Tamil Nadu, India
[3]Department of Laboratory Medicine, Bio Line Research Institute, Coimbatore-641 014, Tamil Nadu, India

*Corresponding author: Dr. P. Pasupathi, Ph.D., Head-Department of Clinical Biochemistry,
Bio Line Research Institute, Coimbatore-641 014 Tamil Nadu, India
Tel: +91 422 4270509 Fax: +91 422 4520099 drppasupathi@gmail.com

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Abstract. Pregnancy is associated with significant but reversible changes in thyroid function tests results, which are among the most profound seen as a result of a normal physiologic state. The present study was carried out to find out alterations in thyroid function tests in each trimester in normal pregnant women as compared to non-pregnant women. **Methods:** A case-control study designed with two groups of women: (1) 75 normal pregnant women randomly selected from the first (25 samples), the second (25 samples), and the third (25 samples) trimesters, and (2) 75 randomly selected non-pregnant healthy female controls. Thyroid function tests were carried out by measuring the serum levels of thyroid stimulating hormone (TSH), free and total thyroxin (FT_4, T_4), and free and total triiodothyronine (FT_3, T_3) by commercially available radio-immunoassay kits. **Results:** We found that mean T_4 increased progressively during pregnancy. Serum levels of T_3 increased in the second trimester and then declined during the third trimester compared with non-pregnant women. We also found that FT_4 strongly decreased during the third trimester. Free T_3 declined in the second and third trimesters. The mean TSH did not significantly differ in the three trimesters compared to the levels of non-pregnant women. Thyroid function tests in pregnancy should be interpreted against gestational age-related reference intervals to avoid misinterpretation of thyroid function during pregnancy.

Keywords. FT_3 • FT_4 • Pregnancy • T_3 • T_4 • TSH

Introduction

Hormone Changes. Normal pregnancy results in a number of important physiological and hormonal changes that alter thyroid function. Pregnancy is associated with significant but reversible changes in thyroid function tests, which are among the most profound seen as a result of a normal physiologic state.[1,2,3,4,5,6] Furthermore, human chronic gonadotropin can stimulate the thyroid gland during the first trimester because of its structural similarity to thyrotrophin (TSH).[7] Thyroid hormones play an important role in embryogenesis and fetal development during pregnancy.[8-10]Therefore, thyroid status is frequently assessed during pregnancy, both to evaluate suspected thyroid abnormalities, and to monitor the status of pre-existing thyroid disease. However, the usual clinical and laboratory assessment can be potentially misleading.

The findings associated with the hypermetabolic state of normal pregnancy can overlap with the clinical signs and symptoms of thyroid disease. Both normal pregnancy, and pregnancy complicated by conditions such as hyperemesis gravidarum, can be associated with thyroid function test changes that strongly suggest hyperthyroidism, in the absence of primary thyroid disease.[5, 11, 12]

Therefore, a local population reference range for thyroid hormones in pregnant women is needed.[13-18] The availability of gestational age-dependent reference intervals for thyroid hormones for local populations should help to avoid the underdiagnosis of hyperthyroidism or the overdiagnosis of hypothyroidism, with inadvertent use of thyroid hormone replacement in later pregnancy. It also allows an accurate interpretation of thyroid hormone test results in complicated pregnancies, in which abnormal thyroid function may occur, such as pre-eclampsia and hyperemesis gravidarum .[13, 15, 18]

Because of these pregnancy-related issues, we designed a cross-sectional case-control study. It involved systematic random sampling to identify alterations in thyroid function test results in each trimester in normal pregnant women as compared to non-pregnant women.

Materials And Methods

Subjects. The case group consisted of 75 pregnant women. They did not have pre-existing thyroid disease, hyperemesis gravidarum, trophoblastic disease, or preclampsia. Twenty-five blood samples were randomly selected from women who were in each of the three trimesters of pregnancy, for a total of 75 samples.

The control group was comprised of 75 randomly selected non-pregnant healthy females of childbearing age. All subjects in both groups were consuming iodide salt. Therefore, no subjects had iodide deficiencies.

Biochemical Investigation. The levels of serum thyroid stimulating hormone (TSH), total triiodothyroxine (T_3), free thyroxine (FT_4), and free triiodothyronine (FT_3) were measured by a Microparticle Enzyme Immunoassay (MEIA) on the AXSYM System (Abbott Laboratories, Abbott Park, USA), while serum total thyroxine (T_4) was measured by the Fluorescence Polarization Immunoassay (FPIA) method on the AXSYM System using standard laboratory methods.

Levels of blood glucose, total cholesterol, urea, and creatinine were determined using a fully automated clinical chemistry analyzer (Hitachi 912, Boehringer Mannheim, Germany).

Statistical Analysis. All data were expressed as mean ± SD of number of experiments. The significance level was set at $p \leq 0.05$. The statistical significance was evaluated by Student's t-test using SPSS version 10.0 (SPSS, Cary, NC, USA).

Result

Demographic characteristics and biochemical parameters of the study population are shown in Table 1. The mean age limit of pregnant women was 28 ± 12 years and that of non-pregnant women was 25 ± 15 years. Pregnant women had a significantly increased body mass index (32 ± 6.2 kg/m^2) compared to non-pregnant women (26 ± 3.4 kg/m^2).

Diabetic subjects were defined as those with a minimum fasting blood glucose concentration >120 mg/dL. Fasting blood glucose was significantly lower in pregnant women compared to non-pregnant women. However, the total cholesterol, urea and creatinine in pregnant women and non-pregnant women did not differ significantly.

Table 2 shows the mean ± SD of the measured thyroid function test results of pregnant and non-pregnant women. We found that in the first and second trimesters, the mean TT_4 levels of pregnant women were not significantly lower. However, in the third trimester, the mean TT_4 increased significantly ($p < 0.001$) above the mean of non-pregnant women.

Table 1. Demographic characteristics and biochemical changes in pregnant and non- pregnant subjects.

Parameter	Non-pregnant women	Pregnant women
Age (years)	25 ± 15	28 ± 12
Sex-Females (%)	75 [100%]	75 [100%]
Body mass index (kg/m2)	26 ± 3.4	32 ± 6.2*
Fasting blood glucose (mg/dl)	92 ± 13	113 ± 27**
Urea (mg/dl)	21 ± 15	28 ± 17^{NS}
Creatinine (mg/dl)	0.6 ± 0.3	0.7 ± 0.4^{NS}
Total cholesterol (mg/dl)	165 ± 15	164 ± 17^{NS}

Values are given as mean ± S.D from seventy-five subjects in each group
Pregnant subjects compared with non- pregnant subjects
(* p<0.05, ** p<0.01, ***p<0.001). NS-Not significant

In the first trimester, the mean TT_3 value did not significantly differ between the two groups of subjects. In the second trimester, however, the mean TT_3 value significantly increased ($p < 0.05$) compared to that of the control group. In the third trimester, the mean TT_3 of pregnant women decreased again and did not significantly differ from that of non-pregnant women.

The mean FT_4 levels in the first and the second trimesters were non-significantly lower than that of the non-pregnant subjects. But in the third trimester, the mean FT_4 significantly decreased ($p < 0.01$) relative to the mean for non-pregnant women.

The pregnant groups' mean FT_3 values declined over the trimesters. In the second and third trimesters, the mean levels of pregnant women were significantly lower ($p < 0.01$) than the mean of non-pregnant women.

In each trimester, the mean TSH levels of pregnant women were lower than the mean level of non-pregnant. In the first and third trimesters, pregnant women's lower TSH levels were not statistically sig-

Table 2. Serum thyroid hormone status in pregnant and non- pregnant subjects.

Parameters	TT4 (nmol/L)	TT3 (nmol/L)	FT4 (pmol/L)	FT3 (pmol/L)	TSH (mIU/ml)
Non-pregnant women N=75	89.75 ± 32.53	2. 95 ± 1.06	15.10 ± 11.56	6.21 ± 3.10	2.54 ± 1.32
Pregnant women N=75					
First trimester (N = 25)	80.78 ± 39.77^{NS}	2.44 ± 1.53^{NS}	14.93 ± 3.77^{NS}	7.11 ± 2.32^{NS}	1.93 ± 1.53^{NS}
Second trimester (N = 25)	93.30 ± 43.60^{NS}	3.41 ± 1.42*	12.78 ± 4.16^{NS}	4.17 ± 1.72**	2.08 ± 1.57*
Third trimester (N = 25)	127.51 ± 52.50***	2.91 ± 1.70^{NS}	7.01 ± 3.70**	3.21 ± 1.56**	2.74 ± 0.91^{NS}
Overall N = 75	107.50 ± 41.25**	3.12 ± 1.81^{NS}	11.91 ± 5.10**	5.25 ± 1.84*	1.99 ± 1.30*

Values are given as mean ± S.D from twenty-five subjects in each group.
Pregnant subjects compared with non- pregnant subjects (* $p<0.05$, ** $p<0.01$, ***$p<0.001$).
^{NS}-Not significant.

nificant, but in the second trimester, pregnant women's mean TSH was significantly lower ($p < 0.05$).

We also compared the mean values of each thyroid function test between pregnant and non-pregnant women (Table 2). We found the following: The mean TT_4 of pregnant women was significantly higher ($p < 0.01$), the FT_4 was significantly lower ($p < 0.01$), the FT_3 was significantly lower ($p < 0.05$), and the mean TSH was significantly lower ($p < 0.05$).

Discussion

This study showed that compared to non-pregnant women, TT_4 rose during the third trimester, whereas TT_3 increased in the second trimester. Free T_4 strongly declined during the third trimester, whereas FT_3 decreased in the second and the third trimesters. Mean TSH rose progressively through the three trimesters of pregnancy, but mean levels in the trimeters did not significantly differ from those of non-pregnant women.

The overall mean of each thyroid function test level was calculated (Table 2). The mean TT_3 did not show a significant difference between pregnant and non-pregnant women. However, the mean TT_4 significantly increased, and the mean FT_4, FT_3, and TSH were significantly lower.

Khandakar et al. performed a case-control study to learn the alterations in serum thyroid hormone levels in normal pregnant women compared to non-pregnant women in Dhaka City.[8] For this purpose, the researchers randomly selected 35 pregnant women during the third trimester and 21 non-pregnant women of childbearing age as controls. Their study showed that the mean serum TT_4 level of non-pregnant women was within the reference range. However, compared to the non-pregnant women, the pregnant women had a significantly higher TT_4 level during the third trimester. This finding was similar to ours in this study.

Khandakar et al.[8] also found that the mean TT_3 levels in the two groups were within the reference range and did not significantly differ. This result contrasts with our finding: in the second trimester, pregnant women in our study had a mean TT_3 level significantly higher than in non-pregnant subjects (Table 2).

The mean TSH level in the Khandakar et al. study was closely similar to what we found. However, a significant limitation of their investigation was a small sample size. Panesar et al. carried out a prospective study with 343 healthy pregnant women (5-41 weeks) and 63 non-pregnant controls. Their purpose was to establish gestation-related reference intervals for thyroid hormones in pregnant Chinese women.[13] They found that the FT_3 decreased during pregnancy, while the FT_4 initially increased, peaking between 9-13 weeks. Then the FT_4 decreased, the decline becoming significant by week 21. The change in TSH level was similar to that of FT_4.

We also found declining FT_3 levels as the women's pregnancies progressed; the highest level was during the first trimester and the lowest in the third. FT_4 changes during pregnancy in our study were similar to those in the study by Panesar et al. In contrast to Panesar et al., we did not find a significant change in the mean TSH level in the first and third trimesters, but in the second trimester, the mean TSH level of pregnant women was significantly lower than that of non-pregnant women ($p < 0.05$). Also, when we calculated the mean TSH level for pregnant women for all three trimesters, it was significantly lower ($p < 0.05$) relative to the mean level of non-pregnant women.

McElduff found that the FT_4 decreased during pregnancy compared to non-pregnant women, and this resulted in the need for each laboratory to develop its own reference range for FT_4 levels in pregnancy.[15]

Our study also showed a progressive lowering of mean FT_4 levels with each trimester during the pregnancies. Kumar A et al. measured serum levels of T_3, T_4, and TSH in 124 pregnant women. The women were apparently normal, healthy young primigravidas with no known metabolic disorders and normal carbohydrate gestational intolerance test.[16] They found that the mean TT_3 increased during the second trimester and then declined in the third trimester compared to the first trimester. We found the same result in our study. Kumar A et al. also showed the mean TT_4 level rose in the second trimester and then decreased during the third trimester. But in our study, the TT_4 increased in both the second and the third trimester.

Kumar et al. also saw that the mean TSH level rose progressively through the trimesters of pregnancy.[16] Our study also showed this increase through the trimesters (Table 2).

Erem et al. investigated maternal thyroid function in 29 pregnant women with goiter and 51 pregnant women without goiter. The location of the women was the eastern black sea region of Turkey, which is an endemic goiter area.[17] They found that TT_4, FT_4, TT_3, FT_3, and thyroxine binding globulin increased during pregnancy. Erem, et al. also found that serum TSH levels declined in pregnant women without goiter compared with nonpregnant women without goiter. In our study, changes in the serum levels of TT_4, TT_3, and TSH in pregnant women were closely similar to those reported by Erem, et al. But in contrast to their findings, we found that serum levels of FT_4 and FT_3 in pregnant women increased compared to those of nonpregnant women.

Mechanisms of Thyroid Hormone Changes in Pregnancy. The etiology of increase in total circulating thyroid hormones primarily involves increased concentrations of plasma thyroxine binding globulin during pregnancy.[7]

Another proposed mechanism for the increased total thyroid hormone concentrations is production of type III deiodinase by the placenta. This enzyme, which converts T_4 to reverse T_3, and T_3 to diiodotyrosine (T_2), has extremely high activity during fetal life. Increased demand for T_4 and T_3 has been suggested to increase production of these hormones which ultimately increases the circulating concentrations of the hormones.[7] Increased sialylation, mediated by oestrogens, reduces the heptic clearance of thyroxine binding globulin, resulting in increased levels of both TT_4 and TT_3.[13] Changes in albumin and free fatty acid concentrations sustain the binding of T_4 and T_3 to carrier proteins; this lowers the blood levels of FT_4 and FT_3 as pregnancy progresses.[12,13]

Conclusion. It is important that thyroid function tests in pregnancy be interpreted against gestational age-related reference intervals. Clinical use of the results of this study could minimize the possibility of the misinterpretation of thyroid function test results of pregnant women in our research area of Coimbatore, Tamil Nadu, India.

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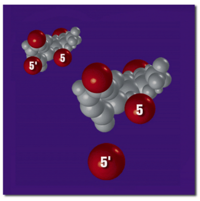

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Study of Thyroid Auto-Antibodies in Patients with Bronchial Asthma and Allergic Rhinitis

Full Text Free in pdf format

Mohammed Fahamy Abd El-Aziz,[1] Maged Mohamed Rafaat,[2]
Inas Mohamed Sabry,[1]* Mohamed Yousef,[3] Amira Mandour[4]

[1]Endocrine and Diabetes Unit, Internal Medicine Department, Ain Shams University,
[2]Allergy Unit, Internal Medicine Department, Ain Shams University,
[3]Clinical Pathology Department, Ain Shams University,
[4]Misr University for Technology and Science, Cairo, Egypt.

*Corresponding Author: Inas Mohamed Sabry Mohamed El Nabrawy MD,
Endocrine unit, Internal Medicine Department, Ain Shams University Hospitals,
Faculty of Medicine, Ain Shams University. Abbassia, Cairo; Egypt.
Address: 8 Nasr Street, 1st May Buildings, Nasr City; Cairo, Egypt.
Tel: +2 0101780318 Fax: +2. 24845647
Email: inassabry27@gmail.com, nancy27eg@yahoo.com

Abstract. Background: Few reports stated that autoimmunity in patients with allergic rhinitis had increased frequency of Grave's disease. Moreover, it had been clarified that the association of seasonal allergic rhinitis was frequent in Grave's disease and rare in painless thyroiditis. Little is known about relation between thyroid disease and allergic diseases. **Aim of the Work:** is to study of coexistence of thyroid auto-antibodies in patients with bronchial asthma and allergic rhinitis. **Methods:** 40 patients with allergic diseases (20 patients with bronchial asthma [BA], and 20 patients with allergic rhinitis [AR]) and 20 healthy control subjects were included in the study. Free triiodothyronine (FT3), free thyroxin (FT4) by radioimmunoassay (RIA) and thyroid stimulating hormone (TSH); Thyroid auto-antibodies [anti-thyroid peroxidase (anti-TPO)and anti-thyroglobulin (anti-TG)] by Enzyme- linked Immunosorbent Assay (ELISA); complete blood picture; allergic skin tests; and peak expiratory flow rate measured by spirometry were done. **Results:** Thyroid auto-antibodies levels were higher in patients with BA and AR in comparison with healthy subjects ($P < 0.05$). While, there was no significant difference as regard thyroid profiles (FT3, FT4, and TSH). Also, there was non significant difference as regards thyroid auto-antibodies were found between BA and AR ($P > 0.05$). **Conclusion:** Autoimmune process may be associated with allergic disease but this is not enough to induce changes in thyroid profiles.

Keywords • Anti-thyroglobulin • Anti-thyroid peroxidase antibody • Allergic diseases • thyroid hormones IgE

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Clinical and Laboratory Studies

Study of Thyroid Auto-Antibodies in Patients with Bronchial Asthma and Allergic Rhinitis

Mohammed Fahamy Abd El-Aziz,[1] Maged Mohamed Rafaat,[2]
Inas Mohamed Sabry,[1]* Mohamed Yousef,[3] Amira Mandour[4]

[1]Endocrine and Diabetes Unit, Internal Medicine Department, Ain Shams University,
[2]Allergy Unit, Internal Medicine Department, Ain Shams University,
[3]Clinical Pathology Department, Ain Shams University,
[4]Misr University for Technology and Science, Cairo, Egypt.

Corresponding Author: *Inas Mohamed Sabry Mohamed El Nabrawy MD,
Endocrine unit, Internal Medicine Department, Ain Shams University Hospitals,
Faculty of Medicine, Ain Shams University. Abbassia, Cairo; Egypt.
Address: 8 Nasr Street, 1st May Buildings, Nasr City; Cairo, Egypt.
Tel: +2 0101780318 Fax: +2. 24845647
Email: inassabry27@gmail.com, nancy27eg@yahoo.com

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Abstract. **Background:** Authors of a few reports have stated that autoimmunity increases the frequency of Grave's disease in some patients with allergic rhinitis. Also, seasonal allergic rhinitis has been reported to be more frequent in Grave's disease but rare in painless thyroiditis. However, little is known about the relation between thyroid disease and allergic diseases. **Aim of Our Work:** Our aim was to study the coexistence of thyroid auto-antibodies in patients with bronchial asthma and allergic rhinitis. **Methods:** Forty patients with allergic diseases (20 patients with bronchial asthma [BA] and 20 patients with allergic rhinitis [AR]) and 20 healthy control subjects were included in the study. We measured the free triiodothyronine (FT_3), free thyroxin (FT_4) by radioimmunoassay (RIA), and thyroid stimulating hormone (TSH); thyroid auto-antibodies (anti-thyroid peroxidase [anti-TPO] and anti-thyroglobulin [anti-TG]) by Enzyme-linked Immunosorbent Assay (ELISA); the complete blood picture; allergic skin tests; and peak expiratory flow rate measured by spirometry. **Results:** Thyroid auto-antibodies levels were higher in patients with BA and AR compared to healthy subjects ($P < 0.05$). However, thyroid function test results (FT_3, FT_4, and TSH) did not significantly differ between patients and controls. Also, thyroid auto-antibodies levels did not significantly differ between patients with BA and those with AR ($P > 0.05$). **Conclusion:** Thyroid auto-immunity was associated with allergic disease but was not reflected in changed thyroid biochemical profiles.

Keywords • Anti-thyroglobulin • Anti-thyroid peroxidase antibody • Allergic diseases • thyroid hormones IgE

Introduction

Allergic disorders are diseases in which the immune system reacts inappropriately to exogenous antigens. In contrast, in autoimmune diseases, reactions are directed against auto-antigens, resulting in different kinds of diseases, depending on which organs are affected. The prevalence of auto-antibodies among allergic patients needs to be studied, since patients prone to react against exogenous antigens may also react more readily to endogenous antigens.[1]

The prevalence of allergic disease is increasing allover the world, but its influence on the clinical course of autoimmune disease in unknown.[2] Also, little is known about the relation between thyroid disease and allergic diseases.[3] Little is also known about the influence of allergic rhinitis, the production of auto-antibodies, and the clinical course of autoimmune disease.

Takeoka and colleagues[3] concluded that seasonal allergic rhinitis aggravated the clinical course of Grave's disease. They wrote that the allergic rhinitis increased both serum anti-thyroid auto-antibodies and the concentration of pollen-specific IgE. Hidaka and co-workers[4] observed that Grave's thyrotoxicosis

Table 1. Comparison between bronchial asthma (BA) versus allergic rhinitis patients (AR) as regard total IgE, thyroid profile and thyroid auto-antibodies by student t-test and Mann Whitney test (#)

Variables	**BA** (n = 20) (Mean±SD)	**AR** (N = 20) (Mean±SD)	**t**	***p* - value**
Free T3 (pg/mL)	2.3 ± 0.7	2.05 ± 0.6	1.1	>0.05 (NS*)
Free T4 (ng/mL)	1.2 ± 0.3	1.3 ± 0.3	1	>0.05 (NS)
TSH (MIU/mL)	1.7 ± 1.6	1.7 ± 1.0	0.1#	>0.05 (NS)
Total IgE	192 ± 101	189 ±144	0.16#	>0.05 (NS)
Anti-thyroglobulin Antibody	20.4 ± 10	16.8 ± 9	1.12#	>0.05 (NS)
Anti-thyroid peroxidase Antibody	15 ± 7.9	15 ± 0.4	5.2	>0.05 (NS)

[1]BA: Bronchial asthma; [2]AR: Allergic rhinitis; [3]NS: nonsignificant.

frequently relapsed or was aggravated after attacks of seasonal allergic rhinitis. Furthermore, Lindberg and coworkers[1] found higher thyroid peroxidase antibodies in children with allergic asthma.

Knowledge of the presence of thyroid disease in patients with bronchial asthma is important. The reason is that hypothyroidism may coexist with allergic diseases such as bronchial asthma,[1] while hyperthyroidism may be associated with a lower incidence of allergies. The association of thyroid disease and allergic diseases may be useful to clinicians who are alerted to the association. To add to the available knowledge base, the aim of our study, was to determine whether thyroid auto-antibodies coexist in patients with bronchial asthma and allergic rhinitis.

Methods and Materials

Our case-control study included 40 patients with different allergic diseases. Twenty patients had bronchial asthma, and 20 patients had allergic rhinitis. We also included 20 healthy controls. All patients abstained from steroid therapy for at least one month before collection of laboratory samples. Each subjects provided a full history and underwent a clinical examination.

Fasting serum samples were collected from all patients and processed within 30 minutes. The samples were kept frozen at -20°C. We assayed levels of free triiodothyronine (FT$_3$), free thyroxine (FT$_4$) by using T$_3$ and T$_4$ Accubind ELISA Microwells (Monobind, Inc. Lake Forest, CA (92630) USA).

For FT$_3$, values between 1.4 and 4.2 ng/dL were considered normal, and for FT$_4$, 0.8 and 2.5 ng/dL were considered normal.

Serum TSH, anti-TG antibodies and anti-TPO antibodies were assessed by using TSH, anti-TG and anti-TPO Accubind ELISA Microwells (Monobind, Inc. Costa Mesa, CA (92627) USA). Values between 0.28 and 5.6 mU/L were consider normal for the TSH. Test results for thyroid autoimmunity were considered positive if anti-TG antibody levels were greater than 125 IU/mL, and for anti-TPO antibody levels greater than 40 IU/mL.

Allergic evaluation included two methods. First was the total serum IgE by ELISA based on the sandwich principle, assessed according to Engvall et al.[5] Second was skin tests using common, environmental, and food antigens on the volar surface of forearm. Grading of the skin prick test was performed according to Saxon.[6]

For each subject, we also included a complete blood picture and neck ultrasonography. Asthmatic patients underwent peak expiratory flow rate measurements according to the method of Haydu et al.[7] and Dworin.[8] Before a subject was included in the study, an informed consent was obtained from each patient. Our study protocol was reviewed and approved by our local institutional human research committee as conforming to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical analysis. Analysis of data was done by IBM computer using SPSS (statistical program for social science, version 12). The following statistical methods were used:

Table 2. Comparison between BA versus controls as regard total IgE, thyroid profile and thyroid autoantibodies by student t-test and Mann Whitney test (#)

Variables	**BA** (n = 20) (Mean±SD)	**Controls** (N = 20) (Mean±SD)	**t**	***p* - value**
FT_3 (pg/mL)	2.3 ± 1.1	1.5 ± 0.4	1.4	> 0.05 (NS[2])
FT_4 (ng/mL)	1.2 ± 0.3	1.3 ± 0.4	0.7	> 0.05 (NS)
TSH (MIU/mL)	1.7 ± 1.6	1.7 ± 0.5	0.9#	> 0.05 (NS)
Total IgE	180 ± 144	14.2 ± 7	5.3#	< 0.01 (HS[3])
Anti-thyroglobulin Antibody	16.84 ± 9	10.3 ± 2.7	3#	< 0.01 (HS)
Anti-thyroperoxidase Antibody	15 ± 5.2	8.3 ± 2.2	5.5	< 0.01 (HS)

[1]BA: bronchial asthma; [2]NS: Nonsignificant; [3]HS: Highly significant.

Description of quantitative variables as means, SDs, and ranges; description of qualitative variables as numbers and percentages; chi-square test for comparisons of qualitative variables between groups; unpaired t-tests to compare two groups, and ANOVA to compare more than two groups regarding quantitative variables in parametric data; the Mann-Whitney Wilcoxon test instead of unpaired t-tests with non-parametric data; Spearman correlation coefficient to rank different variables as either positive or inverse.

The results were considered to be statistically significant at a p value < 0.05, highly significant at a p value < 0.001, and insignificant at a p value > 0.05.

Results

The sixty subjects included in this study were matched by age and gender; the three groups did not significantly differ on these matching variables ($p > 0.05$).

As shown in Table 1, the TSH, FT_3, FT_4, thyroid auto-antibodies and total IgE results of patients with bronchial asthma and allergic rhinitis did not significantly differ ($p > 0.05$). Also, as shown in Tables 2 and 3, there was no significant difference in the TSH, FT_3, FT_4 levels between the two patients groups and the healthy controls healthy subjects ($p > 0.05$).

However, IgE, anti-TG, and anti-TPO antibody levels were significantly higher in patients with allergic diseases than in healthy subjects ($p < 0.01$). The mean anti-TG antibody level was significantly positively correlated with the total IgE level (IU/mL) in bronchial asthma patients ($r = 0.54$, $p < 0.05$). Similarly, the mean anti-thyroglobulin antibody level was significantly positively correlated with the total IgE level (IU/mL) in allergic rhinitis patients ($r = 0.60$, $p < 0.01$), as shown in Figure 1.

In bronchial asthma patients, anti-TG antibody and anti-TPO antibody levels did not significantly correlate with the peak expiratory flow rate (L/m), ($r = 0.08$, $p > 0.05$) and ($r = 0.18$, $p > 0.05$).

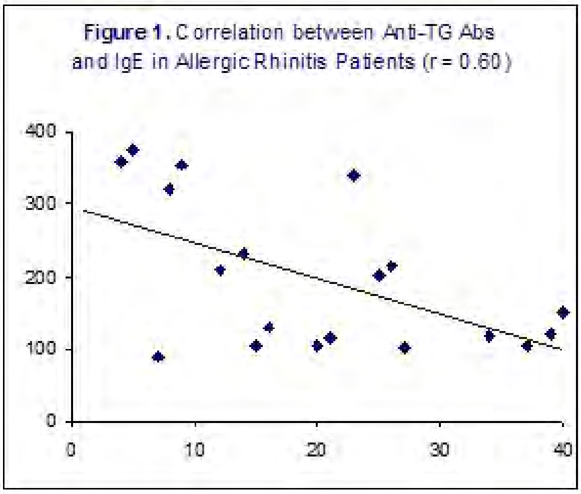


Figure 1. Correlation between Anti-TG Abs and IgE in Allergic Rhinitis Patients (r = 0.60)

Anti-TPO antibody level significantly negatively correlated with the total IgE in allergic rhinitis patients ($r = -0.56$, $p < 0.05$), as shown in Figure 2. But peroxidase antibodies did not correlate with the total IgE in bronchial asthma patients ($r = 0.13$, $p > 0.05$).

The duration of allergic diseases and anti-TG antibody did not correlate among both patients with bronchial asthma ($r = -0.31$, $p > 0.05$) and those with al-

Table 3. Comparison between AR versus controls as regard total IgE, thyroid profile and thyroid autoantibodies by student t-test and Mann Whitney test (#)

Variables	**AR** (n = 20) (Mean ± SD	**Controls** (N = 20) (Mean±SD)	**t**	***p* - value**
FT$_3$ (pg/mL)	2.05 ± 0.6	1.5 ± 0.4	1.9	> 0.05 (NS)
FT$_4$ (ng/mL)	1.3 ± 0.3	1.3 ± 0.4	0.12	> 0.05 (NS)
TSH (MIU/mL)	1.7 ± 1.0	1.7 ± 0.5	0.04#	> 0.05 (NS)
Total IgE	180 ± 144	14.2 ± 7	5.3#	< 0.01 (HS[3])
Anti-thyroglobulin Antibody	16.84 ± 9	10.3 ± 2.7	3#	< 0.01 (HS)
Anti-thyperoxidase Antibody	15 ± 5.2	8.3 ± 2.2	5.5	< 0.01 (HS)

[1]AR: Allergic rhinitis; NS: [2]Nonssignificant; [3]HS: Highly significant.

lergic rhinitis ($r = -0.21$, $p > 0.05$). The duration of allergic disease significantly negatively correlated with anti-TPO ($r = -0.42$, $p < 0.05$) in patients with bronchial asthma, but did not correlate in patients with allergic rhinitis ($r = -0.2$, $p > 0.05$). The anti-TG antibody level significantly positively correlated with the TSH in both bronchial asthma patients ($r = 0.45$, $p < 0.05$) and allergic rhinitis patients ($r = 0.25$, $p < 0.05$). Anti-TPO antibody levels did not significantly correlate with the TSH level of either patients with bronchial asthma ($r = 0.13$, $p > 0.05$) or allergic rhinitis ($r = 0.11$, $p > 0.05$).

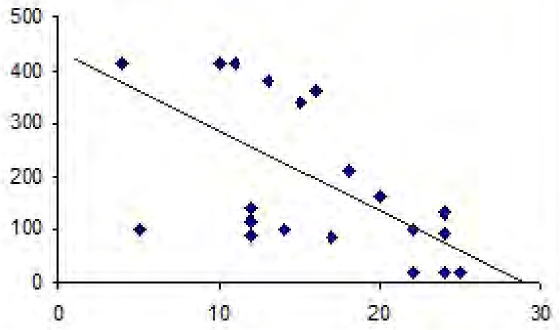
Discussion

The prevalence of auto-antibodies among allergic patients merits study. The reason is that patients who are prone to react to exogenous antigens may also react more readily to endogenous antigens.[1]

In the present study, there was a significant statistical difference between the serum total IgE level of healthy subjects and those of patients with bronchial asthma and allergic rhinitis ($p < 0.01$). But no statistically significant difference was found between patients with bronchial asthma and those with allergic rhinitis ($p > 0.05$). These results agree with those of Takeoka and colleagues[2] who recorded a statistically significant elevation of serum total IgE in allergic patients. In addition, Hamilton and Adkinson[9] reported finding no statistically significant difference between the IgE levels was patients with bronchial asthma and those with allergic rhinitis. IgE levels were elevated in 40% of allergic rhinitis patients and 60% of bronchial asthma patients.

On the other hand, in our study, we did not find a significant statistical difference between the FT$_3$, FT$_4$, and TSH levels of patients with bronchial asthma and those with allergic rhinitis ($p > 0.05$). Also, the thyroglobulin and peroxidase antibody levels between the two groups of patients with allergic diseases did not significantly ($p > 0.05$).

Figure 2. Correlation between Anti-TPO Abs and IgE in Allergic Rhinitis Patients (r = -0.56).



Among patients with severe bronchial asthma, thyroglobulin and peroxidase antibodies were elevated. This result suggests that environmental antigens may induce not only local allergic reactions but also stimulate thyroid autoimmune reactions with stimulation of Th2 proliferation in Graves' patients and an aggravation of their Th2-dependent autoimmune thyroid disease.[2]

Anti-TPO and anti-TG antibodies in both our bronchial asthma patients and allergic rhinitis patients were statistically higher than in healthy subjects ($p <$ 0.01). These results were in agreement with Lindberg et al.,[1] and Amino et al.[10] who described an increased incidence of thyroid auto-antibodies in patients with bronchial asthma and/or allergic rhinitis. The explanation was that the Th2 response enhanced antibodies as in allergies, and involved IL4, IL5, and IL13 that stimulate B cells to secrete thyroid antibodies, which in turn decrease thyroid hormone synthesis and secretion.[11]

In our study, however, we found no statistically significant difference ($p > 0.05$) between the FT_3, FT_4, and TSH levels of the two allergic groups and healthy subjects. This finding is contrary to that of Landyshev et al.[12] who reported that thyroid function undergoes biphasic changes in bronchial asthma patients. The also reported that as patients with mild bronchial asthma progressed to paroxysmal exacerbation of their asthma, hypofunction of the patients' thyroid glands developed.[12] Biscaldi et al.[13] reported that FT_3 and T_4 levels were higher in a control group than in asthmatic patients; but still, the asthmatic patients' thyroid hormone levels were within the reference range, suggesting that asthma was not associated with changes in thyroid function.

Conclusion

From our study results, thyroid auto-antibody levels were higher in patients with bronchial asthma and allergic rhinitis. But we found no statistically significant difference between the FT_3, FT_4, and TSH levels of the two groups of allergic patients and those of our healthy control subjects. Our results suggest that thyroid autoimmune processes may be associated with allergic disease, but the processes do not induce changes in TSH and thyroid hormone profile. We recommend larger studies for further evaluation.

Coauthors' Participation

All authors of this report shared equally in patient selection, definitions of intellectual content, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review.

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Assessment of Thyroid Function and Leptin Hormone in Women with Hyperemesis Gravidarum

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Hussein Abdel Hai El Orabi,[1] Inas Mohamed Sabry,[1]
Ahmed Mohamed Awad Allah,[2] Alshymaa Alsayed Abd Alkhalek[1]

[1]Department of Internal Medicine; Endocrine Unit,
[2]Department of Gynecology and obstetric,
Ain Shams University; Cairo, Egypt

*Corresponding Author: Inas Mohamed Sabry Mohamed El Nabrawy MD,
Endocrine unit, Internal Medicine Department, Ain Shams University Hospitals,
Faculty of Medicine, Ain Shams University. Abbassia, Cairo, Egypt.
Address: 8 Nasr Street, 1st May Buildings, Nasr City, Cairo, Egypt.
Tel: +2 0101780318 Fax: +2. 24845647
Email: inassabry27@gmail.com, nancy27eg@yahoo.com

Abstract. Background. Several studies have suggested that hyperemesis gravidarum in early pregnancy is related to women's levels of thyroid hormones, human chorionic gonadotropin (hCG), and serum leptin. To ascertain this relationship, we investigated 50 pregnant women in the first trimester. Twenty subjects had morning sickness, 20 had hyperemesis gravidarum, and 10 were healthy pregnant women who served as control subjects. **Methods.** The enzyme immunoassay method was used to measure all subjects' serum levels of T3 (pg/mL), T4 (ng/dL), TSH (μIU/mL), antithyroid peroxidase (anti-TPO) antibodies (IU/ml), and leptin (ng/mL). Serum β hCG was quantitatively assayed. **Results.** There was a statistically significant difference between the three studied groups as regards serum free T4 ($p < 0.05$), but there was no difference as regards serum free T3, TSH, anti-TPO, and serum β-hCG ($p > 0.05$). Serum leptin was significantly higher ($p < 0.001$) in the hyperemesis gravidarum and vomiting group compared to the healthy control group, with a non-significant difference between pregnant women with hyperemesis gravidrum and those with vomiting ($p > 0.05$). Correlation analysis showed that the only significant positive correlation was between serum T3 and serum leptin ($p < 0.05$) in hyperemesis gravidarum. No significant correlation was found between β-hCG and thyroid hormones, antithyroid antibodies, and serum leptin in pregnant women with morning sickness and hyperemesis gravidarum ($p > 0.05$). **Conclusion.** Our results suggest that serum leptin levels are involved in the pathogenesis of hyperemesis gravidarum. No significant role was detected for thyroid hormones, serum β-hCG, or anti-TPO in patients with hyperemesis gravidarum.

Keywords • Hyperemesis gravidarum • hCG • Leptin • Pregnancy • T3 • T4 • Thyroid hormone

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Clinical and Laboratory Studies

Assessment of Thyroid Function and Leptin Hormone in Women with Hyperemesis Gravidarum

Hussein Abdel Hai El Orabi,[1] Inas Mohamed Sabry,[1]
Ahmed Mohamed Awad Allah,[2] Alshymaa Alsayed Abd Alkhalek[1]

[1]Department of Internal Medicine; Endocrine Unit,
[2] Department of Gynecology and obstetric,
Ain Shams University; Cairo, Egypt

Corresponding author: Inas Mohamed Sabry Mohamed El Nabrawy MD,
Endocrine unit, Internal Medicine Department, Ain Shams University Hospitals,
Faculty of Medicine, Ain Shams University. Abbassia, Cairo, Egypt,
Address: 8 Nasr Street, 1st May Building, Nasr City, Cairo, Egypt.
Tel: +2 0101780318 Fax: +2 24845647 inassabry27@gmail.com nancy27eg@yahoo.com

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***Abstract.* Background.** Several studies have suggested that hyperemesis gravidarum in early pregnancy is related to women's levels of thyroid hormones, human chorionic gonadotropin (hCG), and serum leptin. To ascertain this relationship, we investigated 50 pregnant women in the first trimester. Twenty subjects had morning sickness, 20 had hyperemesis gravidarum, and 10 were healthy pregnant women who served as control subjects. **Methods.** The enzyme immunoassay method was used to measure all subjects' serum levels of T_3 (pg/mL), T_4 (ng/dL), TSH (μIU/mL), antithyroid peroxidase (anti-TPO) antibodies (IU/ml), and leptin (ng/-mL). Serum β hCG was quantitatively assayed. **Results.** There was a statistically significant difference between the three studied groups as regards serum free T_4 ($p < 0.05$), but there was no difference as regards serum free T_3, TSH, anti-TPO, and serum β-hCG ($p > 0.05$). Serum leptin was significantly higher ($p < 0.001$) in the hyperemesis gravidarum and vomiting group compared to the healthy control group, with a non-significant difference between pregnant women with hyperemesis gravidrum and those with vomiting ($p > 0.05$). Correlation analysis showed that the only significant positive correlation was between serum T_3 and serum leptin ($p < 0.05$) in hyperemesis gravidarum. No significant correlation was found between β-hCG and thyroid hormones, antithyroid antibodies, and serum leptin in pregnant women with morning sickness and hyperemesis gravidarum ($p > 0.05$). **Conclusion.** Our results suggest that serum leptin levels are involved in the pathogenesis of hyperemesis gravidarum. No significant role was detected for thyroid hormones, serum β-hCG, or anti-TPO in patients with hyperemesis gravidarum.

Keywords • Hyperemesis gravidarum • hCG • Leptin • Pregnancy • T_3 • T_4 • Thyroid hormone

INTRODUCTION

Hyperemesis gravidarum is a condition of intractable vomiting during pregnancy, leading to fluid, electrolyte and acid–base imbalance, nutritional deficiency, and weight loss often severe enough to require hospital admission.[1] Hyperemesis gravidarum is most prevalent during, but certainly not limited to, the first trimester of pregnancy when both the placenta and the corpus luteum are producing hormones and the body is adapting to the pregnancy state.[2]

Estimates of the incidence of hyperemesis gravidarum vary from 0.3 to 1.5% of all live births, with most authors reporting an incidence of 0.5%.[3,4] It is said to be higher in multiple pregnancies, hydatidiform mole, and other conditions associated with increased pregnancy hormone levels.[2]

Up to 80% of all pregnant women experience some form of nausea and vomiting during their pregnancies.[5] Because the great majority of pregnant women experience discomfort due to nausea and vomiting, a functional role of nausea and vomiting is often considered. Despite decades of research, the cause of these conditions remains unknown, and the relationship between nausea and vomiting during pregnancy and hyperemesis gravidarum is still unclear.[2] Many

etiopathogenic factors have been considered for hyperemesis gravidarum, including endocrine factors, hepatic dysfunction, changes in lipid metabolism, upper gastrointestinal system dysmotility, and psychological factors. However, no specific causative factor has been established.[6] Theories on how pregnancy hormones could cause hyperemesis gravidarum assert that patients who develop the condition may be exposed to higher levels of hormones during early pregnancy, especially progesterone and hCG. Also, irrespective of the gestational week, the rapid increase in the leptin concentrations in the first trimester may be a factor and also an early marker for hyperemesis gravidarum.[6]

Sometimes, thyroid hormone values deviate from the reference range, leading to a state referred to as gestational transient thyrotoxicosis (GTT). This has been observed in up to two thirds of women suffering from hyperemesis gravidarum.[7]

The etiology of transient hyperthyroidism of hyperemesis gravidarum is unclear. Some have argued that the hyperthyroidism is the cause of hyperemesis, whereas others have argued the reverse. The aim of this study was to evaluate the thyroid function, serum β-hCG, and serum leptin in women with hyperemesis gravidarum.

MATERIALS AND METHODS

A case-control study was conducted involving 50 pregnant women in their first trimester of pregnancy. The women were selected from the outpatient clinic of Maternity Clinic and the in-patient wards of the Hospital of Obstetric and Gynecology at Ain Shams University Hospitals. The patients were divided into three groups. The first group was patients with emesis (vomiting); the second group was patients with hyperemesis gravidarum [defined as persistent nausea and vomiting associated with ketosis and weight loss > 5% of pre-pregnancy weight];[8] and the third group was healthy pregnant women who served as controls.

All groups were adjusted for age, parity, and BMI. All included women were subjected to the following: full history taking, thorough clinical examination; measurement of serum TSH (µIU/mL) by electrochemiluminescence immunoassay (ECLIA); serum FT_3 (pg/mL), serum FT_4 (ng/dL), and anti-thyroid peroxidase (Anti-TPO)(IU/mL) by micro particle enzyme immunoassay (MEIA); serum β-human chorionic gonadotrophins (serum β-hCG) quantitatively by the Sandwich principle; serum leptin (ng/mL) by ELISA technique (normal value of serum leptin level is: < 50 ng/ml);[9] and blood urea (mg/dL), serum creatinine (mg/dL), serum sodium (mmol/l), serum potassium (mmol/L), and complete blood picture to detect the severity of emesis.

A blood sample of 15 cc was withdrawn from each subject and the blood sample was divided in the following way:

(a) 5 cc were used for a thyroid profile (TSH, FT_3, FT_4, and Anti-TPO);
(b) 5 cc were were collected and stored as serum in an aliquot at -20°C till time of assay for serum leptin.
(c) 5cc were used for blood electrolytes and urea, and serum creatinine and β-hCG (quantitative).

Also, ketones in a morning urine sample were measured with urine stripes.

Statistical Analysis. Data were collected, revised, verified, and then edited on a PC. Then data were analyzed statistically using SPSS statistical package, version 15. Data were expressed as mean ± SD for quantitative measures. The following tests were done:

1. The Student's-t test for independent variables and was used to assess significant differences between values in various groups of patients where appropriate.
2. ANOVA test was used for comparison between more than two independent groups as regard studied variables.
3. *Post hoc* test was used for comparison of quantitative variables.
4. Pearson correlation coefficient (r) was done for correlations between different studied parameters.
5. Sensitivity, specificity, and diagnostic accuracy at different cut-off levels and ROC-curves were analyzed.

The results were considered to be statistically significant at a p value of < 0.05, highly significant at p value of < 0.001, and insignificant at *a* p value of > 0.05.

RESULTS

As shown in Table 1, the only statistically significant differences between the three studied groups were in regard to the free T_4 and serum leptin ($p < 0.05$). The β-hCG level was higher in patients with hyperemesis gravidarum than in women with emesis and healthy controls, but the difference was not significant ($p > 0.05$). *Post hoc* testing for comparisons

of the three studied groups showed a significantly higher mean free T_4 level for group 2 compared to group 1 and group 3 ($p < 0.05$). But as shown in Table 2, the difference in the free T_4 level between group 1 and group 3 was not significant ($p > 0.05$). Also, the difference in leptin levels between the the emesis group and the hyperemesis gravidarum group was not significant ($p > 0.05$). However, the leptin levels in both the emesis group and hyperemesis gravidarum group were highly significantly higher than the level in the healthy control group ($p < 0.00$).

Table 1. The comparative data of all studied groups by ANOVA test.

Parameters	**Group (1)** (Pregnant with emesis)	**Group (2)** (Pregnant with hyperemesis gravidum)	**Group (3)** (Healthy pregnant control)	F	P	Sig
	N = 20	N = 20	N = 10			
FT$_3$ (pg/mL)	2.5 ± 0.5	2.6 ± 0.6	2.4 ± 0.5	0.6	> 0.05	NS
FT$_4$ (ng/dL)	***1 ± 0.1***	***1.3 ± 0.5***	***1 ± 0.2***	***4.1***	***< 0.05***	***S***
TSH(µIU/mL)	2.1 ± 1	1.4 ± 1.5	1.8 ± 0.9	1.9	> 0.05	NS
Anti-TPO (IU/mL)	6.4 ± 4.8	15.2 ± 29.2	5.1 ± 2.6	1.5	> 0.05	NS
β-hCG (mIU/mL)	79.7 ± 54.6	93.4 ± 57.8	69.5 ± 60.2	0.8	> 0.05	NS
Leptin (ng/mL)	**37.5 ± 28.8**	**43.6 ± 6.1**	***16.2 ± 9.2***	***9***	***< 0.00***	***HS***

NS=non significant, S= significant, HS= highly significant, N= number

Pearson correlation tests for the emesis group and the healthy control group, respectively, showed no significant correlation of serum leptin and serum β-hCG (r: 0.107) (r: 0.198), anti-TPO (r: 0.029) (r: -0.590), free T_4 (r: 0.145) (r: 0.287), and free T_3 (r: 0.322) (r: -0.374) ($p > 0.05$). In the hyperemesis gravidarum group, the serum leptin level was positively correlated with the free T_3 with an r value of 0.551 (Figure 1).

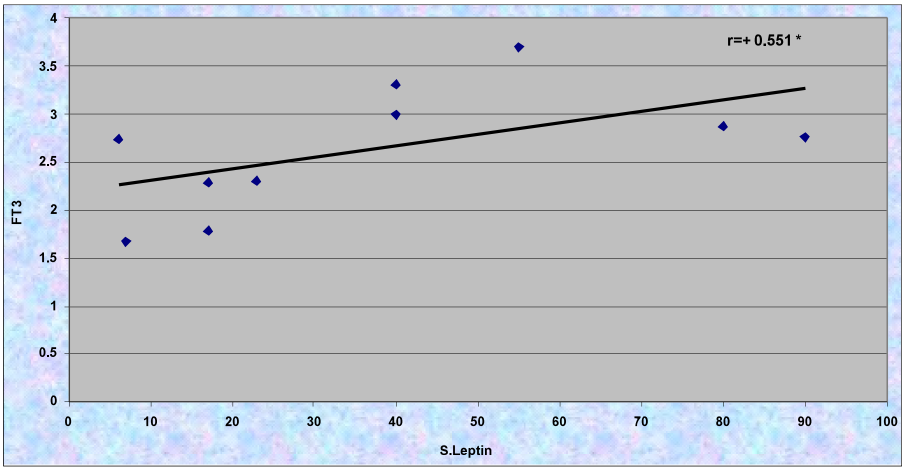

Figure 1. Correlation between serum leptin and FT3 in hyperemesis gravidarum.

In the healthy control group, the leptin level was significantly negatively correlated with the serum TSH ($r = -0.737$, $p < 0.05$). Also, in this group, the serum β-hCG level was positively correlated with the free T_3 level ($r = 0.755$, $p < 0.05$).

In the emesis group and the hyperemesis gravidarum group, respectively, no correlation ($p > 0.05$) was found between the levels of serum β-hCG and anti-TPO (r: -0.146) (r: 0.021), serum leptin (r: 0.367((r: 0.107) [Figure 2], TSH (r: 0.344) (r:

-0.212), free T_4 (*r*: -0.248) (*r*: -0.312), and free T_3 (*r*: 0.050) (*r*: -0.359). Serum anti-TPO was positively correlated only with the free T_3 (*r*: 0.587) and the free T_4 (*r*: 0.938) in hyperemesis gravidarum group ($p < 0.01$) and the TSH (*r*: 0.447) in the emesis group ($p < 0.05$).

Table 2. A multiple comparison study between all studied by *post hoc* test.

Parameters	Group (1) vs Group (2)			Group (1) vsGroup (3)			Group (2) vs Group (3)		
	LSD	P	Sig.	LSD	P	Sig.	LSD	P	Sig.
FT_3 (pg/mL)	-0.113	> 0.05	NS	0.111	> 0.05	NS	0.224	> 0.05	NS
FT_4 (ng/dL)	***-0.268***	***< 0.05***	***S***	-0.011	> 0.05	NS	***0.257***	***< 0.05***	***S***
TSH (µIU/mL)	0.719	> 0.05	NS	0.357	> 0.05	NS	-0.362	> 0.05	NS
Anti-TPO (IU/mL)	-8.82	> 0.05	NS	1.315	> 0.05	NS	10.135	> 0.05	NS
β-hCG (mIU/mL)	23.96	> 0.05	NS	13.765	> 0.05	NS	-10.195	> 0.05	NS
Leptin (ng/mL)	-6.100	> 0.05	NS	***-21.300***	***< 0.00***	***HS***	***-27.400***	***< 0.00***	***HS***

NS=non significant, S= significant, HS= highly significant, N= number

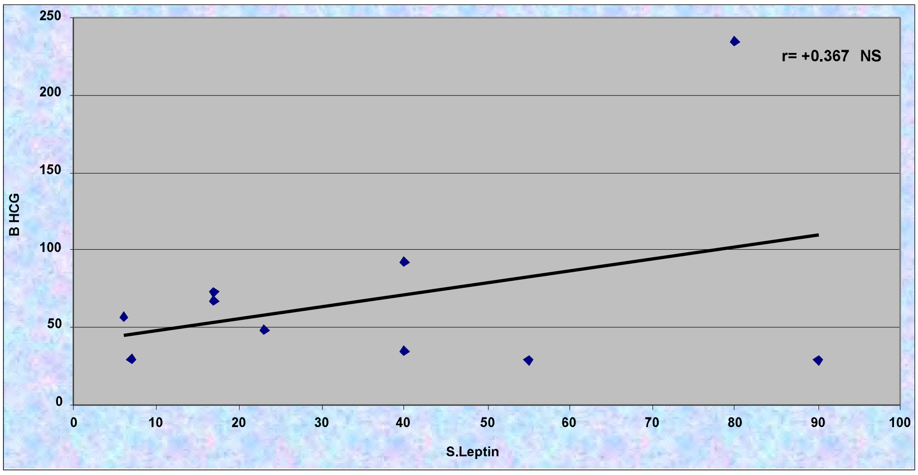

Figure 2. Non-significant correlation between serum leptin and β hCG in hyperemesis Gravidarum.

For the hyperemesis gravidarum group, the ROC curve detected the best cutoff point for the free T_4: 1.06 ng/dL, with a sensitivity = 80% and a specificity = 80 % and an area under the curve of 0.743 with a *p* value of < 0.004. But there was not a significant cut off point for serum leptin with a *p* value of > 0.05, a sensitivity = 60%, and a specificity = 53.3%.

DISCUSSION

Hyperemesis gravidarum is defined as excessive vomiting during pregnancy, which may lead to sever outcomes including weight loss, dehydration, fasting acidosis, alkalosis due to hydrochloric acid loss, and hypokalemia.[10] Both the etiology and pathogenesis of hyperemesis gravidarum remain unknown.[2] The potential role of pregnancy-related hormones such as progesterone, estrogen, and hCG has been widely studied; however, various other hormones such as leptin, placental growth hormone, prolactin, thyroid hormone, and adrenal-cortical hormones have been implicated in the etiology of hyperemesis gravidarum.

The presence of an association between hyperemesis gravidarum and the rapid increase in leptin of placental origin, particularly in the first trimester, may be considered.[6] This study aimed to study thyroid hormones, serum β-hCG, anti-TPO, and serum leptin in women with hyperemesis gravidarum, and to detect any possible role of these parameters in the pathogenesis of hyperemesis gravidarum.

Our study revealed that there was no significant difference between the three studied groups as regards the free T_3, TSH, and anti-TPO ($p > 0.05$). Only the

free T_4 was significantly higher in the hyperemesis gravidarum group compared with the emesis group and the healthy control group ($p < 0.05$). However, the higher free T_4 was still within reference range.

The higher reference range free T_4 level in the hyperemesis gravidarum group can be explained by the characteristic pattern of serum free T_4 changes during normal pregnancy.

This pattern includes a slight and temporary rise in the free T_4 during the first trimester (due to the thyrotropic effect of hCG) and a tendency for serum free T_4 values to decrease progressively during later gestational stages.[11] But, although we found that the serum β-hCG level was higher in the hyperemesis gravidarum group than in the emesis group and the healthy control group, the level was not significantly different ($p > 0.05$).

This finding agrees with Al-Yatama et al.[12] They found that the serum free T_4 level was higher in hyperemesis gravidarum patients than in healthy controls ($p < 0.0001$), but no patients showed signs of thyrotoxicosis. We detected that the best significant cut off point of free T_4 for women with hyperemesis gravidarum was 1.06 ng/dL with a sensitivity = 80% and a specificity = 80% with a p value of < 0.004), which is still within the reference range for the free T_4. Panesar et al.[13] found by logistic regression analysis that the free thyroxine level was an independent variable. In addition, they found no significant difference between the free T_4 levels of healthy pregnant women and those with emesis ($p > 0.05$). Kimura et al.[14] found that serum free T_4 and free T_3 levels were higher in pregnant women with emesis and hyperemesis gravidarum ($p < 0.01$) and that the serum TSH was suppressed to less than 0.1mU/L in both groups. They also found, as we did in this study, that the serum β-hCG level did not significantly differ between the emesis group, hyperemesis gravidarum group, and the healthy control group. Also, Wilson et al.[15] reported no significant difference between the thyroid hormone and hCG levels of healthy controls and hyos peremesis gravidarum patients. In addition, Panesar et al.[13] observed that hGC is not independeetiology of hyperemesis gravidarum. In contrast, however, Al-Yatama et al.[12] reported that the total β-hCG level was significantly higher in hyperemesis gravidarum patients than in healthy control subjects.

Tan et al.[16] found that hyperemesis gravidarum patients were not clinically overtly thyrotoxic and thyroid antibodies were usually absent. But Taskin et al.[17] reported that the serum TSH and serum β-hCG levels were higher in women with hyperemesis gravidarum than in healthy pregnant women, while there was no significant difference between the groups as regards free T_3 and T_4 levels. However, Asakura et al.[18] found that free T_3 and free T_4 levels were significantly higher in hyperemesis gravidarum patients than in healthy controls; the levels were higher in the hyperemesis gravidarum patients with milder symptoms of morning sickness ($p < 0.05$). Also, Leylek et al.[19] found that the mean serum hCG, free T_3, and free T_4 levels were significantly higher in hyperemesis gravidarum patients than in healthy controls ($p < 0.05$), with a non-significant difference in serum TSH levels ($p > 0.05$). They also found that for hyperemesis gravidarum patients, the serum hCG significantly negatively correlated with the TSH and positively correlated with the free T_3 and free T_4. They found no relationship between β-hCG and thyroid function test levels in the control group ($p > 0.05$).

Our study did not show a significant correlation between serum β-hCG and serum TSH, free T_3, and free T_4 levels in hyperemesis gravidarum patients. In healthy controls, only the β-hCG level was positively correlated with the free T_3 ($r = 0.755$, $p < 0.05$). Tareen et al.,[20] demonstrated that serum T_4 and β-hCG were significantly increased in hyperemesis gravidarum, while the TSH significantly declined in the same group. They also found a direct relationship between the serum T_4 and β-hCG levels and an inverse relationship between the TSH and β-hCG levels in pregnant women with morning sickness.

Goodwin et al.[21] observed that the hCG level correlated directly with the free T_4 level and inversely with the TSH level ($p < 0.001$) in women with hyperemesis gravidarum. They also found that patients with hyperemesis gravidarum had significantly higher mean levels of free T_4, hCG, and total T_3, and a lower TSH level compared to control subjects. From these results, it was suggested that hyperemesis gravidarum may be caused by some not-yet-identified circulating stimulator. Abell and Riely,[22] suggested that there is a circulating hormone or hormone-like substance that may stimulate the thyroid gland and render it temporarily unresponsive to the control of the pituitary. This suggests that thyroid hormones are stimulated by something other than the TSH. By the time this substance subsides in later pregnancy, both the hyperemesis gravidarum and the hyperthyroidism resolve.

The serum leptin levels significantly differed ($p < 0.00$) between our three studied groups: the emesis and hyperemesis gravidarum groups had higher leptin levels than the healthy control group. However, the difference between women with emesis and hyperemesis gravidarum was not significant ($p > 0.05$). This agrees with Nurettin et al.[6] who found that their

group with hyperemesis gravidarum had significantly a higher serum leptin level ($p = 0.037$) than healthy pregnant women. But thyroid hormones and hCG levels in the two groups did not significantly differ.

In the hyperemesis gravidarum group in our study, only the serum leptin level positively correlated with the free T_3 level ($p < 0.05$). But three prospective cohort studies that compared the serum leptin levels between hyperemesis gravidarum patients and controls did not show a statistically significant difference.[23,24,25] Supporters of the leptin theory stated that this could be a false negative finding due to a negative energy balance in hyperemesis gravidarum patients, a dramatic decrease in leptin levels being observed in other condition with a negative energy balance, such as fasting.[26,27,28]

Our data show that patients with hyperemesis gravidarum had a significantly higher free T_4 level, but the level was within the reference range and the patients had no clinical manifestations of thyrotoxicosis. The group therefore had no underlying thyroid abnormality. It appears that neither thyroid hormones nor hCG contribute to the pathogenesis of hyperemesis gravidarum. Serum leptin, however, may play a role in the pathogenesis of hyperemesis gravidarum. Larger studies are needed to confirm this role.

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Thyroid Science 3(2):CLS1-2, 2008

Fine-Needle Aspiration of the Thyroid Gland—Its Role in the Investigation of Thyroid Autoimmunity

(Full Text Free in pdf format)

P.O. Sandberg, MD, PhD*

*Aleris Medilab, Täby Sweden *Contact:* christina.sandberg@erol.se

Introduction*

John C. Lowe, MA, DC, Editor-in-Chief

In a September 2007 editorial, I described the important clinical work and research on autoimmune thyroiditis that Dr. Bo Wikland and his colleagues are conducting in Stockholm, Sweden. Since the editorial, Dr. Wikland has generously written two papers for *Thyroid Science.* In his first paper, he describes hypothyroidism caused by autoimmune thyroiditis in patients with "normal" blood test results, a condition he and his colleagues call "subchemical hypothyroidism." In his second paper, he presents an important hypothesis: that with these patients—who are clinically hypothyroid, biochemically euthyroid, but have laboratory evidence of autoimmune thyroiditis—we must suppress their TSH levels to stop the pathological activity in the thyroid gland and relieve their symptoms.

Now we are privileged to publish a highly informative paper that dovetails with his. It is written by Dr. P.O. Sandberg, a clinical and research colleague of Dr. Wikland's in Stockholm. Dr. Sandberg is a cytopathologist. In working with Dr. Wikland, he examines thyroid gland tissue samples in her laboratory for evidence of autoimmune thyroid disease.

In his paper, Dr. Sandberg explains the importance of examining tissue samples for structural evidence of autoimmune disease. He also shows us, in a photograph of lymphocyte-invaded thyroid tissues, what he often sees in tissue samples from afflicted patients.

Dr. Sandberg comments on the relative contributions of different procedures used in the diagnostic workups of thyroiditis patients. He discusses the features to look for during palpation of the thyroid gland, and what ultrasound may reveal both before and during its use in guiding fine-needle aspiration.

Dr. Sandberg's paper provides an extraordinary learning opportunity for those of us who haven't spent time with a cytopathologist in his or her lab. Most importantly, though, is that he makes clear the importance of fine-needle aspiration and the need for the involvement of more cytopathologists in patients' diagnostic workups. We are grateful to him for contributing this important paper to *Thyroid Science*.

Keywords. Autoimmune thyroid disease • Chronic fatigue • Cytopathology • Fine-needle aspiration • Ultrasonography

*Thanks to our Executive Editor, Jackie Yellin, for enabling us to expeditiously publish Dr. Sandberg's paper.

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Its Role in the Investigation of Thyroid Autoimmunity.
Thyroid Science, 3(2):CLS1-2, 2008.

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Thyroid Science 3(2):CLS1-2, 2008 www.ThyroidScience.com *Clinical and Lab Studies*

Fine-Needle Aspiration of the Thyroid Gland—Its Role in the Investigation of Thyroid Autoimmunity

P.O. Sandberg, MD, PhD*

*Aleris Medilab, Täby Sweden *Contact*: christina.sandberg@erol.se

Keywords: Autoimmune thyroid disease • Fine-needle aspiration • Ultrasonography

The procedure of examining the thyroid by fine-needle aspiration (FNA) cytology is widely adopted. However, its use is mostly restricted to the investigation of an enlarged gland with or without nodular lesions, the objective being to rule out malignancy.

FNA of the thyroid is useful in other clinical settings such as the demonstration of invasion of lymphocytes in autoimmune disease. This application of FNA has old traditions in Stockholm, Sweden. A pioneer in this field was Torsten Löwhagen,[1] who refined the technique and extended it to many other organs.

As a successor cytologist, I work in cooperation with Dr. Bo Wikland. We have elaborated a simple and effective algorithm for the diagnostic workup of the chronically fatigued patient. Our basic objective is to ascertain whether the patient is a victim of symptomatic autoimmune thyroiditis (AT). In this context, a cytomorphologic finding of unequivocal AT is considered to be the gold standard—the most convincing evidence of autoimmune affection of the thyroid gland.

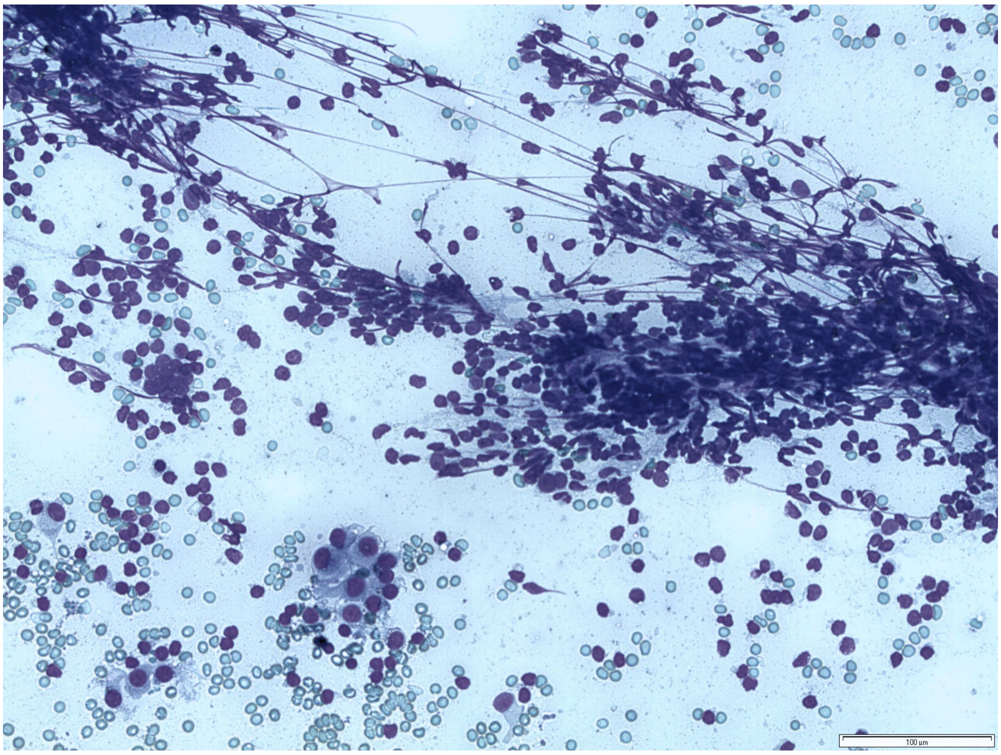

Figure 1. Thyroid epithelium with Hürteloid metaplasia and an increase and infiltration of lymphocytes due to autoimmune response.

Figure 1 shows an FNA specimen. In addition to a background of colloid and a varying amount of follicular epithelium, there is an invasion of lymphocytes. In cases of long-standing autoimmune affection, the follicular epithelium may undergo so-called Hürtheloid metaplasia. In representative specimens, I expect at least 3 follicular complexes infiltrated by lymphocytes, and a background of varying amount of lymphocytes.

In the typical case, there is little doubt of the diagnosis of AT. As is so often in biomedical sciences, there are borderline cases with uneven distribution of cytomorphological elements representing autoimmunity. Therefore, in case of uncertainty, repeat examination may be necessary—in particular, in the absence of convincing biochemical/serological evidence of thyroid autoimmunity. Uniform cytomorphological criteria of thyroid autoimmunity would be welcome (e.g., a minimum number of lymphocytes per visual field). Ideally, the importance of documenting thyroid autoimmunity would increase demand for more cytologists; this in turn, would help generate broad consensus documents.

Since 1998, we have performed 8416 thyroid FNA examinations in our laboratory. Of these, the main finding was AT in 1746 (21%).[2]

It is essential to examine the thyroid gland, regardless of its size. Careful palpation may provide useful information. A tender and/or firm gland suggests inflammation/scarring.

Ultrasonography (US) is of value in the examination of a low-volume gland. A small/atrophic thyroid usually represents end-stage AT, a finding mostly encountered in patients over the age of 60.

US can also support a diagnosis of active AT. The experienced examiner will frequently observe an irregular echogenicity. We see small nodules (less than 10 mm in diameter) in about 70% of patients with AT; the nodules rarely call for further investigation. US-directed FNA may be of value in cases where previously aspired material is insufficient for diagnosis.

As we have reported earlier, compared with biochemical and serological assessment alone, and in terms of diagnostic sensitivity, the morphological approach is superior for documenting symptomatic AT.[3][4] In the clinical setting of a patient with strongly suspected symptomatic AT, whose conventional biochemical tests/thyroid antibody assays fail to provide evidence in support of the clinical suspicion, FNA may cytomorphologically document AT. FNA, being an already well-accepted procedure, is a valuable tool (in addition to the evaluation of thyroid nodules) for documenting thyroid autoimmunity, and as such merits wider recognition.

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Subcellular Levels of L-T$_3$ and L-T$_4$ in Adult Rat Brain Cerebral Cortex

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Pradip K Sarkar, PhD, MSc, BSc (Honors)

Department of Basic Sciences, Parker College of Chiropractic
2500 Walnut Hill Lane, Dallas, Texas 75229, USA

**Correspondence*: Dr. Pradip K. Sarkar,
Telephone: 972-438-6932 Extension: 7336 Fax: 214-902-2448
E-mail: psarkar@parkercc.edu

***Abstract*. Background.** Thyroid hormones exert major well-known functions in the growth and differentiation of most types of mammalian tissues. The hormones exert these effects via interaction with nuclear thyroid-hormone receptors, which regulate target gene expression. Thyroid dysfunctions in adult individuals have been linked to several neuropsychological disorders that can be corrected by appropriate adjustments of circulating thyroid hormones. However, the actions of thyroid hormones in the mature brain are unclear. As the mammalian brain approaches adulthood, thyroid hormone concentrations within nuclei decrease and in nerve terminals increase. These ontogenic differences and the changes in the subcellular localization and concentration of thyroid hormones are important in the exploration of thyroid hormone function in the adult mammalian brain.**Aim.** The aim of the present study was to compare the concentrations of L-triiodothyronine (L-T3) and L-tetraiodothyronine (L-T4) in two preparations from adult rat brain.**Procedure.** L-T3 and L-T4 concentrations were determined by radioimmunoassay. Comparisons were made of the concentrations of the hormones in two different preparations derived from young adult rat brain cerebral cortex: (1) purified synaptosomes (an artificial preparation of a subcellular fraction considered to have most biological properties of nerve terminals) and (2) non-synaptic mitochondria. **Results.** The concentration of L-T3 was found to be ~3-fold higher in non-synaptic mitochondria compared to synaptosomal L-T3 concentrations. The assay used did not detect L-T4 in either fraction. **Conclusion.** The higher concentrations of L-T3 compared to L-T4 in the two different prepared fractions indicates a pivotal biological role of L-T3 in adult mammalian brain

Keywords• Cerebral cortex • L-T3 • L-T4 • Mitochondria • Ontogeny • Synaptosome

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Subcellular Levels of L-T3 and L-T4 in Adult Rat Brain Cerebral Cortex

Pradip K Sarkar, PhD, MSc, BSc (Honors)

Department of Basic Sciences, Parker College of Chiropractic
2500 Walnut Hill Lane, Dallas, Texas 75229, USA

Correspondence: Dr. Pradip K. Sarkar,
Telephone: 972-438-6932 Extension: 7336 Fax: 214-902-2448
E-mail: psarkar@parkercc.edu

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Abstract. **Background.** Thyroid hormones exert major well-known functions in the growth and differentiation of most types of mammalian tissues. The hormones exert these effects via interaction with nuclear thyroid-hormone receptors, which regulate target gene expression. Thyroid dysfunctions in adult individuals have been linked to several neuropsychological disorders that can be corrected by appropriate adjustments of circulating thyroid hormones. However, the actions of thyroid hormones in the mature brain are unclear. As the mammalian brain approaches adulthood, thyroid hormone concentrations within nuclei decrease and in nerve terminals increase. These ontogenic differences and the changes in the subcellular localization and concentration of thyroid hormones are important in the exploration of thyroid hormone function in the adult mammalian brain. **Aim.** The aim of the present study was to compare the concentrations of L-triiodothyronine (L-T_3) and L-tetraiodothyronine (L-T_4) in two preparations from adult rat brain. **Procedure.** L-T_3 and L-T_4 concentrations were determined by radioimmunoassay. Comparisons were made of the concentrations of the hormones in two different preparations derived from young adult rat brain cerebral cortex: (1) purified synaptosomes (an artificial preparation of a subcellular fraction considered to have most biological properties of nerve terminals) and (2) non-synaptic mitochondria. **Results.** The concentration of L-T_3 was found to be ~3-fold higher in non-synaptic mitochondria compared to synaptosomal L-T_3 concentrations. The assay used did not detect L-T_4 in either fraction. **Conclusion.** The higher concentrations of L-T_3 compared to L-T_4 in the two different prepared fractions indicates a pivotal biological role of L-T_3 in adult mammalian brain.

Keywords • Cerebral cortex • L-T_3 • L-T_4 • Mitochondria • Ontogeny • Synaptosome

INTRODUCTION

Thyroid hormones have well-known vital functions in growth, differentiation, and development of almost all types of mammalian tissues including the brain. The classical mechanism of thyroid hormone action involves interactions with their specific nuclear receptors which in turn regulate target gene expression.[1] Through an offset of this mechanism, dysthyroidism adversely affects the developing brain, causing abnormal neuronal development that can lead to cretinism or myxedema in humans. Hypo- or hyperthyroidism, thus, leads to impairment of normal brain function in neonates. Thyroid disorders in adult humans have been shown to have several clinical neuropsychological, and behavioral adverse effects. Proper adjustment of circulatory thyroid hormone concentrations reduces or relieves these symptoms while the underlying neural mechanism remains unclear.

Immunocytochemical localization studies have shown that thyroid hormone receptors in adult vertebrates are highly concentrated within the choroid plexus, dentate gyrus, hippocampus, amygdaloid complex, pyriform cortex, granular layer of cerebellum, mammillary bodies, and the medial geniculate bodies. Although specific nuclear receptors for thyroid hormone in adult brain have been identified, their function in relation to target gene expression is not yet completely clear. As the brain approaches adulthood, the nuclear iodothyronine level gradually declines and then reaches and maintains a plateau, and in adult vertebrates, thyroid hormone levels increase within nerve terminals.[2]

These switching differences in thyroid hormone ontogeny between developing and adult vertebrate brain has gradually come to interest investigators in their search for new functional roles and mechanisms of thyroid hormone action. Recently the concept of nongenomic actions of thyroid hormones has become popular.[3,4] The functional role of thyroid hormones in adult mammalian brain remains to be clearly understood.

Thyroid hormones are also concentrated and metabolized within nerve terminals of adult rat brain, particularly within synaptosomes, which are a artificial and nucleus-free sub-cellular fraction prepared from adult rat brain.[5-8] However, determination of the concentration of thyroid hormones in other subcellular compartments is needed. To help meet this need, the study reported here quantified and compared the levels of L-T_3 and L-T_4 in purified synaptosomes and non-synaptic mitochondria prepared from adult rat brain cerebral cortex.

METHODS

Animals. Three-month old adult male Charles Foster rats were maintained in a temperature-controlled room (24 ± 1°C) with a 12 h light-dark cycle, and fed ad libitum with a standard rat diet.

Preparation of synaptosomes and non-synaptic mitochondria. The animals were sacrificed quickly by decapitation. The brains were removed and the cerebral cortices were dissected out in an ice-cold condition. The synaptosomes from the cerebral cortex were prepared as described elsewhere.[9] Briefly, the cerebral cortex was homogenized (10 % w/v) in 0.32 M sucrose and centrifuged at 1000 X g for 10 minutes to remove cell debris and nuclei. The supernatant was collected and re-centrifuged at 1000 X g for another 10 minutes. The resulting supernatant was layered over 1.2 M sucrose and centrifuged at 34,000 X g for 50 minutes at 4°C. The fraction collected between the 0.32 M and 1.2 M sucrose layer was diluted at a 1:1.5 ratio with ice-cold bi-distilled water, further layered on 0.8 M sucrose, and again centrifuged at 34,000 X g for 30 minutes. The pellet thus obtained was washed and re-pelleted at 20,000 X g for 20 minutes. Intact synaptosomes were used for the experiments. The bottom pellet in the tube in 1.2 M sucrose was collected, suspended in 5 ml of 0.32 M sucrose and centrifuged at 10,000 X g for 20 minutes and. The washed pellet was used as non-synaptic mitochondria. For the assay of thyroid hormone concentrations, both of the subcellular fractions, the synaptosomes and non-synaptic mitochondria, were repelleted and ruptured hypo-osmotically by resuspending the pellets in ice-cold double-distilled water in ice for 30 minutes with occasional vortexing each 3 minutes.

Radioimmunoassay. Radioimmunoassay (RIA) of the total L-thyroxine (L-T_4) and total L-triiodothyronine (L-T_3) concentrations in serum, synaptosomes, and non-synaptic mitochondria were determined using an RIA kit supplied by Diagnostic Products Corporation, California, USA. All the samples were analyzed in triplicate in four separate experiments. The sensitivity of the L-T_4 and L-T_3 assay were 0.25 g/dL and 7 ng/dL, respectively, of the samples based on 90% B/B_0 intercept where B is the corrected average of standard/sample, and B_0 is the corrected average count of zero standard.

The L-T_4 assay kit showed only 2% cross reactivity with L-T_3 and triiodothyroacetic acid. The L-T_3 assay kit showed 0.38%, 1.1 %, and 0.014% cross reactivity with L-T_4, D-T_4, and reverse-T_3, respectively. Eighty-five to ninety percent of the hormones added to the ruptured subcellular fractions were recovered with the RIA kits. The RIA kit reagents contained 8-anilino naphthosulphonic acid that makes L-T_3 and L-T_4 free from the protein bound form. Hence, the chances for nonspecific binding of the hormone with the subcellular proteins were minimum. This is a direct procedure to measure the thyroid hormone concentrations within brain tissues without prior extraction of the hormones as followed in other conventional RIA methods.

Protein concentrations were measured by the method of Vera[10] using bovine serum albumin as the standard.

Statistical Analysis. Results were expressed as mean SEM of three separate observations. Each observation was made from 4 rats. Statistical analyses of the data were made by performing Student's t-test with $p < 0.05$ as the significance cut-off point.

Results

Comparison of the levels of L-T_4 and L-T_3 in subcellular fractions. Serum levels of L-T_4 and L-T_3 were normal. With this assay system, L-T_4 could not be detected in either synaptosomal or non-synaptic mitochondrial fractions. However, the L-T_3 concentration in synaptosomes and non-synaptic mitochondria was appreciable. The concentration of L-T_3 in non-synaptic mitochondria was 3.2-fold higher than in the synaptosomal fraction purified from cerebral cortices (Table 1).

Table 1. Subcellular levels of thyroid hormones.

Hormones	Serum (ng/ml)	Synaptosome (ng/mg protein)	Non-synaptic Mitochondria (ng/mg protein)
L-T4	41 ± 0.2	ND*	ND*
L-T3	0.7 ± 0.03	0.45 ± 0.06	1.44 ± 0.12

*N.D. = Not Detectable

Discussion

Thyroid dysfunctions in adult humans are known to cause several neuropsychiatric diseases, some of which have been responsive to thyroid hormone therapy. For example, thyroid hormone deficiency has been linked to depressive illness, unipolar depression, affective disorders, and mental dysfunctions.[2]

Recent molecular mechanisms have demonstrated a crucial role of thyroid hormones in signal transduction in the adult brain. The signal transduction is mediated through protein phosphorylation/dephosphorylation.[11-13] The regulation of protein phosphorylation and dephosphorylation, including the involvement of second messenger molecules, have intense implications for thyroid dysfunctions in the adult mammalian central nervous system. Determination and distribution of brain tissue concentrations of thyroid hormones are thus important to understanding the mechanisms of thyroid hormone action in adult humans.

The present report quantifies the thyroid hormone concentrations from adult rat brain synaptosomes and non-synaptic mitochondria. Although L-T_4 levels could not be detected in synaptosomal and non-synaptic fractions, fair amounts of L-T_3 were detected in these fractions purified from adult rat brain cerebral cortex.[6] The finding of undetectable levels of synaptosomal L-T_4 is consistent with the finding in other studies.[7,14,15]

Type II iodothyronine 5’-deiodinase enzyme (5’-DII) is responsible for the conversion of L-T_4 to L-T_3 and appears to be more active in hypothyroidism. Despite low serum levels of thyroid hormone in hypothyroidism, L-T_3 production in the brain has been reported to be very high during stresses such as hypothyroidism.[6] 5’-DII has also been shown to be activated during other types of stresses, apparently playing a protective role in stressed brain.[16] Stimulated levels of 5’-DII has also been described during hypothyroidism, and this supports the initial report[6] of elevated brain L-T_3 concentrations during n-propylthiouracil-induced hypothyroidism.[7,8]

In the brain, approximately 80% of the L-T_3 is produced locally from L-T_4 by 5’-DII. The fractional rate of conversion of L-T_4 to L-T_3 is high in brain.[17,18] This might be a possible cause for undetectable L-T4 concentrations in the fractions used in this study. To detect endogenous thyroid hormones, the subcellular fractions were ruptured hypo-osmotically. The use of 8-anilinonaphtho-sulfonic acid in the RIA medium excluded the possibility of the non-detectable protein bound form of thyroid hormone by releasing the endogenously bound form of the hormones.

A comparison between the subcellular fractions tested showed that the L-T_3 levels in the non-synaptic mitochondrial fraction were ~3.2-fold higher than in the synaptosomal fractions. Levels of L-T_4 remained undetected. Comparatively higher levels of L-T_3 in the mitochondria may have implications for mitochondrial energetics, such as cellular oxygen consumption, oxidative phosphorylation, and ATP synthesis, which is one of the major regulatory functions of thyroid hormone.[19] Thyroid hormones have also been shown to affect the mitochondrial genome. Its effects are mediated by imported isoforms of nuclear thyroid hormone receptors that bind thyroid hormones, especially L-T_3 and L-T_2, and influence various mitochondrial transcription factors.[3]

The localization and concentration of radiolabeled L-T_3 within nerve terminals was the first landmark research described in adult rat brain.[20] This was followed by the immunohistochemical mapping that demonstrated that locus ceruleus norepinephrine stimulate the active conversion of L-T_4 to L-T_3. This established a morphologic co-localization of central thyronergic and noradrenergic systems.[5] Overall thyroid hormone levels within different compartments of the brain might be found to have discrete, differential, and potential regulatory functions for neurotransmission within adult mammalian brain.

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Clinical and Laboratory Studies

Assessment of Thyroid Function and Leptin Hormone in Women with Hyperemesis Gravidarum

Hussein Abdel Hai El Orabi,[1] Inas Mohamed Sabry,[1]
Ahmed Mohamed Awad Allah,[2] Alshymaa Alsayed Abd Alkhalek[1]

[1]Department of Internal Medicine; Endocrine Unit,
[2] Department of Gynecology and obstetric,
Ain Shams University; Cairo, Egypt

Corresponding author: Inas Mohamed Sabry Mohamed El Nabrawy MD,
Endocrine unit, Internal Medicine Department, Ain Shams University Hospitals,
Faculty of Medicine, Ain Shams University. Abbassia, Cairo, Egypt,
Address: 8 Nasr Street, 1st May Building, Nasr City, Cairo, Egypt.
Tel: +2 0101780318 Fax: +2 24845647 inassabry27@gmail.com nancy27eg@yahoo.com

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***Abstract.* Background.** Several studies have suggested that hyperemesis gravidarum in early pregnancy is related to women's levels of thyroid hormones, human chorionic gonadotropin (hCG), and serum leptin. To ascertain this relationship, we investigated 50 pregnant women in the first trimester. Twenty subjects had morning sickness, 20 had hyperemesis gravidarum, and 10 were healthy pregnant women who served as control subjects. **Methods.** The enzyme immunoassay method was used to measure all subjects' serum levels of T_3 (pg/mL), T_4 (ng/dL), TSH (µIU/mL), antithyroid peroxidase (anti-TPO) antibodies (IU/ml), and leptin (ng/-mL). Serum β hCG was quantitatively assayed. **Results.** There was a statistically significant difference between the three studied groups as regards serum free T_4 ($p < 0.05$), but there was no difference as regards serum free T_3, TSH, anti-TPO, and serum β-hCG ($p > 0.05$). Serum leptin was significantly higher ($p < 0.001$) in the hyperemesis gravidarum and vomiting group compared to the healthy control group, with a non-significant difference between pregnant women with hyperemesis gravidrum and those with vomiting ($p > 0.05$). Correlation analysis showed that the only significant positive correlation was between serum T_3 and serum leptin ($p < 0.05$) in hyperemesis gravidarum. No significant correlation was found between β-hCG and thyroid hormones, antithyroid antibodies, and serum leptin in pregnant women with morning sickness and hyperemesis gravidarum ($p > 0.05$). **Conclusion.** Our results suggest that serum leptin levels are involved in the pathogenesis of hyperemesis gravidarum. No significant role was detected for thyroid hormones, serum β-hCG, or anti-TPO in patients with hyperemesis gravidarum.

Keywords • Hyperemesis gravidarum • hCG • Leptin • Pregnancy • T_3 • T_4 • Thyroid hormone

INTRODUCTION

Hyperemesis gravidarum is a condition of intractable vomiting during pregnancy, leading to fluid, electrolyte and acid–base imbalance, nutritional deficiency, and weight loss often severe enough to require hospital admission.[1] Hyperemesis gravidarum is most prevalent during, but certainly not limited to, the first trimester of pregnancy when both the placenta and the corpus luteum are producing hormones and the body is adapting to the pregnancy state.[2]

Estimates of the incidence of hyperemesis gravidarum vary from 0.3 to 1.5% of all live births, with most authors reporting an incidence of 0.5%.[3,4] It is said to be higher in multiple pregnancies, hydatidiform mole, and other conditions associated with increased pregnancy hormone levels.[2]

Up to 80% of all pregnant women experience some form of nausea and vomiting during their pregnancies.[5] Because the great majority of pregnant women experience discomfort due to nausea and vomiting, a functional role of nausea and vomiting is often considered. Despite decades of research, the cause of these conditions remains unknown, and the relationship between nausea and vomiting during pregnancy and hyperemesis gravidarum is still unclear.[2] Many

etiopathogenic factors have been considered for hyperemesis gravidarum, including endocrine factors, hepatic dysfunction, changes in lipid metabolism, upper gastrointestinal system dysmotility, and psychological factors. However, no specific causative factor has been established.[6] Theories on how pregnancy hormones could cause hyperemesis gravidarum assert that patients who develop the condition may be exposed to higher levels of hormones during early pregnancy, especially progesterone and hCG. Also, irrespective of the gestational week, the rapid increase in the leptin concentrations in the first trimester may be a factor and also an early marker for hyperemesis gravidarum.[6]

Sometimes, thyroid hormone values deviate from the reference range, leading to a state referred to as gestational transient thyrotoxicosis (GTT). This has been observed in up to two thirds of women suffering from hyperemesis gravidarum.[7]

The etiology of transient hyperthyroidism of hyperemesis gravidarum is unclear. Some have argued that the hyperthyroidism is the cause of hyperemesis, whereas others have argued the reverse. The aim of this study was to evaluate the thyroid function, serum β-hCG, and serum leptin in women with hyperemesis gravidarum.

MATERIALS AND METHODS

A case-control study was conducted involving 50 pregnant women in their first trimester of pregnancy. The women were selected from the outpatient clinic of Maternity Clinic and the in-patient wards of the Hospital of Obstetric and Gynecology at Ain Shams University Hospitals. The patients were divided into three groups. The first group was patients with emesis (vomiting); the second group was patients with hyperemesis gravidarum [defined as persistent nausea and vomiting associated with ketosis and weight loss > 5% of pre-pregnancy weight];[8] and the third group was healthy pregnant women who served as controls.

All groups were adjusted for age, parity, and BMI. All included women were subjected to the following: full history taking, thorough clinical examination; measurement of serum TSH (μIU/mL) by electrochemiluminescence immunoassay (ECLIA); serum FT_3 (pg/mL), serum FT_4 (ng/dL), and anti-thyroid peroxidase (Anti-TPO)(IU/mL) by micro particle enzyme immunoassay (MEIA); serum β-human chorionic gonadotrophins (serum β-hCG) quantitatively by the Sandwich principle; serum leptin (ng/mL) by ELISA technique (normal value of serum leptin level is: < 50 ng/ml);[9] and blood urea (mg/dL), serum creatinine (mg/dL), serum sodium (mmol/l), serum potassium (mmol/L), and complete blood picture to detect the severity of emesis.

A blood sample of 15 cc was withdrawn from each subject and the blood sample was divided in the following way:

(a) 5 cc were used for a thyroid profile (TSH, FT_3, FT_4, and Anti-TPO);
(b) 5 cc were were collected and stored as serum in an aliquot at -20°C till time of assay for serum leptin.
(c) 5cc were used for blood electrolytes and urea, and serum creatinine and β-hCG (quantitative).

Also, ketones in a morning urine sample were measured with urine stripes.

Statistical Analysis. Data were collected, revised, verified, and then edited on a PC. Then data were analyzed statistically using SPSS statistical package, version 15. Data were expressed as mean ± SD for quantitative measures. The following tests were done:

1. The Student's-t test for independent variables and was used to assess significant differences between values in various groups of patients where appropriate.
2. ANOVA test was used for comparison between more than two independent groups as regard studied variables.
3. *Post hoc* test was used for comparison of quantitative variables.
4. Pearson correlation coefficient (r) was done for correlations between different studied parameters.
5. Sensitivity, specificity, and diagnostic accuracy at different cut-off levels and ROC-curves were analyzed.

The results were considered to be statistically significant at a p value of < 0.05, highly significant at p value of < 0.001, and insignificant at *a* p value of > 0.05.

RESULTS

As shown in Table 1, the only statistically significant differences between the three studied groups were in regard to the free T_4 and serum leptin ($p < 0.05$). The β-hCG level was higher in patients with hyperemesis gravidarum than in women with emesis and healthy controls, but the difference was not significant ($p > 0.05$). *Post hoc* testing for comparisons

of the three studied groups showed a significantly higher mean free T_4 level for group 2 compared to group 1 and group 3 ($p < 0.05$). But as shown in Table 2, the difference in the free T_4 level between group 1 and group 3 was not significant ($p > 0.05$). Also, the difference in leptin levels between the the emesis group and the hyperemesis gravidarum group was not significant ($p > 0.05$). However, the leptin levels in both the emesis group and hyperemesis gravidarum group were highly significantly higher than the level in the healthy control group ($p < 0.00$).

Table 1. The comparative data of all studied groups by ANOVA test.

Parameters	**Group (1)** (Pregnant with emesis)	**Group (2)** (Pregnant with hyperemesis gravidum)	**Group (3)** (Healthy pregnant control)	F	P	Sig
	N = 20	N = 20	N = 10			
FT_3 (pg/mL)	2.5 ± 0.5	2.6 ± 0.6	2.4 ± 0.5	0.6	> 0.05	NS
FT_4 (ng/dL)	***1 ± 0.1***	***1.3 ± 0.5***	***1 ± 0.2***	***4.1***	***< 0.05***	***S***
TSH(µIU/mL)	2.1 ± 1	1.4 ± 1.5	1.8 ± 0.9	1.9	> 0.05	NS
Anti-TPO (IU/mL)	6.4 ± 4.8	15.2 ± 29.2	5.1 ± 2.6	1.5	> 0.05	NS
β-hCG (mIU/mL)	79.7 ± 54.6	93.4 ± 57.8	69.5 ± 60.2	0.8	> 0.05	NS
Leptin (ng/mL)	**37.5 ± 28.8**	**43.6 ± 6.1**	***16.2 ± 9.2***	***9***	***< 0.00***	***HS***

NS=non significant, S= significant, HS= highly significant, N= number

Pearson correlation tests for the emesis group and the healthy control group, respectively, showed no significant correlation of serum leptin and serum β-hCG (r: 0.107) (r: 0.198), anti-TPO (r: 0.029) (r: -0.590), free T_4 (r: 0.145) (r: 0.287), and free T_3 (r: 0.322) (r: -0.374) ($p > 0.05$). In the hyperemesis gravidarum group, the serum leptin level was positively correlated with the free T_3 with an r value of 0.551 (Figure 1).

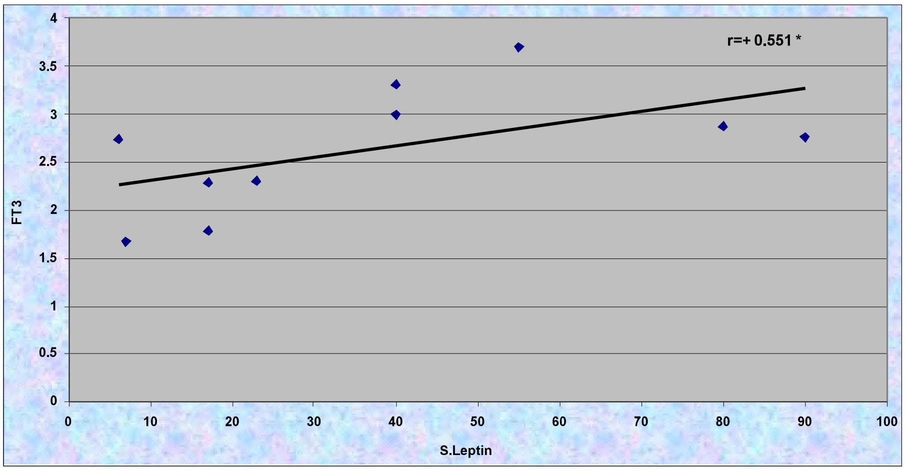

Figure 1. Correlation between serum leptin and FT3 in hyperemesis gravidarum.

In the healthy control group, the leptin level was significantly negatively correlated with the serum TSH ($r = -0.737$, $p < 0.05$). Also, in this group, the serum β-hCG level was positively correlated with the free T_3 level ($r = 0.755$, $p < 0.05$).

In the emesis group and the hyperemesis gravidarum group, respectively, no correlation ($p > 0.05$) was found between the levels of serum β-hCG and anti-TPO (r: -0.146) (r: 0.021), serum leptin (r: 0.367((r: 0.107) [Figure 2], TSH (r: 0.344) (r:

-0.212), free T_4 (*r*: -0.248) (*r*: -0.312), and free T_3 (*r*: 0.050) (*r*: -0.359). Serum anti-TPO was positively correlated only with the free T_3 (*r*: 0.587) and the free T_4 (*r*: 0.938) in hyperemesis gravidarum group ($p <$ 0.01) and the TSH (*r*: 0.447) in the emesis group (p < 0.05).

For the hyperemesis gravidarum group, the ROC curve detected the best cutoff point for the free T_4: 1.06 ng/dL, with a sensitivity = 80% and a specificity = 80 % and an area under the curve of 0.743 with a *p* value of < 0.004. But there was not a significant cut off point for serum leptin with a *p* value of > 0.05, a sensitivity = 60%, and a specificity = 53.3%.

Table 2. A multiple comparison study between all studied by *post hoc* test.

Parameters	Group (1) vs Group (2)			Group (1) vsGroup (3)			Group (2) vs Group (3)		
	LSD	P	Sig.	LSD	P	Sig.	LSD	P	Sig.
FT_3 (pg/mL)	-0.113	> 0.05	NS	0.111	> 0.05	NS	0.224	> 0.05	NS
FT_4 (ng/dL)	***-0.268***	***< 0.05***	***S***	-0.011	> 0.05	NS	***0.257***	***< 0.05***	***S***
TSH (µIU/mL)	0.719	> 0.05	NS	0.357	> 0.05	NS	-0.362	> 0.05	NS
Anti-TPO (IU/mL)	-8.82	> 0.05	NS	1.315	> 0.05	NS	10.135	> 0.05	NS
β-hCG (mIU/mL)	23.96	> 0.05	NS	13.765	> 0.05	NS	-10.195	> 0.05	NS
Leptin (ng/mL)	-6.100	> 0.05	NS	***-21.300***	***< 0.00***	***HS***	***-27.400***	***< 0.00***	***HS***

NS=non significant, S= significant, HS= highly significant, N= number

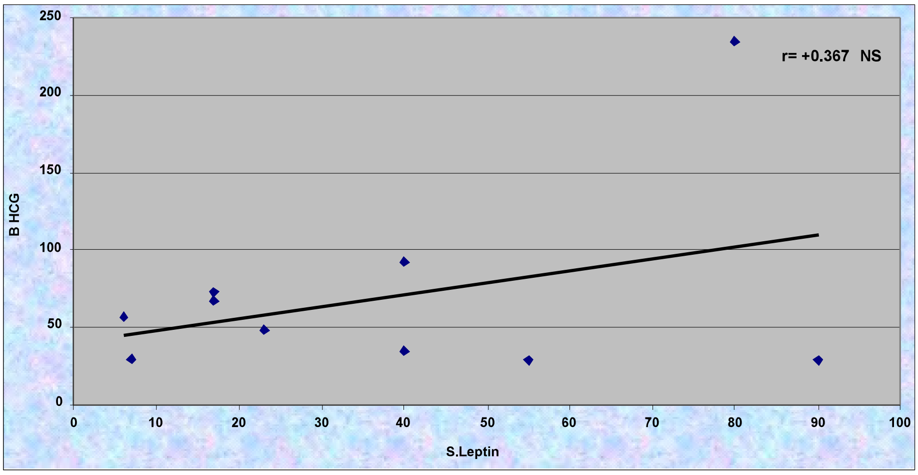

Figure 2. Non-significant correlation between serum leptin and β hCG in hyperemesis Gravidarum.

Discussion

Hyperemesis gravidarum is defined as excessive vomiting during pregnancy, which may lead to sever outcomes including weight loss, dehydration, fasting acidosis, alkalosis due to hydrochloric acid loss, and hypokalemia.[10] Both the etiology and pathogenesis of hyperemesis gravidarum remain unknown.[2] The potential role of pregnancy-related hormones such as progesterone, estrogen, and hCG has been widely studied; however, various other hormones such as leptin, placental growth hormone, prolactin, thyroid hormone, and adrenal-cortical hormones have been implicated in the etiology of hyperemesis gravidarum.

The presence of an association between hyperemesis gravidarum and the rapid increase in leptin of placental origin, particularly in the first trimester, may be considered.[6] This study aimed to study thyroid hormones, serum β-hCG, anti-TPO, and serum leptin in women with hyperemesis gravidarum, and to detect any possible role of these parameters in the pathogenesis of hyperemesis gravidarum.

Our study revealed that there was no significant difference between the three studied groups as regards the free T_3, TSH, and anti-TPO ($p > 0.05$). Only the

free T_4 was significantly higher in the hyperemesis gravidarum group compared with the emesis group and the healthy control group ($p < 0.05$). However, the higher free T_4 was still within reference range.

The higher reference range free T_4 level in the hyperemesis gravidarum group can be explained by the characteristic pattern of serum free T_4 changes during normal pregnancy.

This pattern includes a slight and temporary rise in the free T_4 during the first trimester (due to the thyrotropic effect of hCG) and a tendency for serum free T_4 values to decrease progressively during later gestational stages.[11] But, although we found that the serum β-hCG level was higher in the hyperemesis gravidarum group than in the emesis group and the healthy control group, the level was not significantly different ($p > 0.05$).

This finding agrees with Al-Yatama et al.[12] They found that the serum free T_4 level was higher in hyperemesis gravidarum patients than in healthy controls ($p < 0.0001$), but no patients showed signs of thyrotoxicosis. We detected that the best significant cut off point of free T_4 for women with hyperemesis gravidarum was 1.06 ng/dL with a sensitivity = 80% and a specificity = 80% with a p value of < 0.004), which is still within the reference range for the free T_4. Panesar et al.[13] found by logistic regression analysis that the free thyroxine level was an independent variable. In addition, they found no significant difference between the free T_4 levels of healthy pregnant women and those with emesis ($p > 0.05$). Kimura et al.[14] found that serum free T_4 and free T_3 levels were higher in pregnant women with emesis and hyperemesis gravidarum ($p < 0.01$) and that the serum TSH was suppressed to less than 0.1mU/L in both groups. They also found, as we did in this study, that the serum β-hCG level did not significantly differ between the emesis group, hyperemesis gravidarum group, and the healthy control group. Also, Wilson et al.[15] reported no significant difference between the thyroid hormone and hCG levels of healthy controls and hyos peremesis gravidarum patients. In addition, Panesar et al.[13] observed that hGC is not independeetiology of hyperemesis gravidarum. In contrast, however, Al-Yatama et al.[12] reported that the total β-hCG level was significantly higher in hyperemesis gravidarum patients than in healthy control subjects.

Tan et al.[16] found that hyperemesis gravidarum patients were not clinically overtly thyrotoxic and thyroid antibodies were usually absent. But Taskin et al.[17] reported that the serum TSH and serum β-hCG levels were higher in women with hyperemesis gravidarum than in healthy pregnant women, while there was no significant difference between the groups as regards free T_3 and T_4 levels. However, Asakura et al.[18] found that free T_3 and free T_4 levels were significantly higher in hyperemesis gravidarum patients than in healthy controls; the levels were higher in the hyperemesis gravidarum patients with milder symptoms of morning sickness ($p < 0.05$). Also, Leylek et al.[19] found that the mean serum hCG, free T_3, and free T_4 levels were significantly higher in hyperemesis gravidarum patients than in healthy controls ($p < 0.05$), with a non-significant difference in serum TSH levels ($p > 0.05$). They also found that for hyperemesis gravidarum patients, the serum hCG significantly negatively correlated with the TSH and positively correlated with the free T_3 and free T_4. They found no relationship between β-hCG and thyroid function test levels in the control group ($p > 0.05$).

Our study did not show a significant correlation between serum β-hCG and serum TSH, free T_3, and free T_4 levels in hyperemesis gravidarum patients. In healthy controls, only the β-hCG level was positively correlated with the free T_3 ($r = 0.755$, $p < 0.05$). Tareen et al.,[20] demonstrated that serum T_4 and β-hCG were significantly increased in hyperemesis gravidarum, while the TSH significantly declined in the same group. They also found a direct relationship between the serum T_4 and β-hCG levels and an inverse relationship between the TSH and β-hCG levels in pregnant women with morning sickness.

Goodwin et al.[21] observed that the hCG level correlated directly with the free T_4 level and inversely with the TSH level ($p < 0.001$) in women with hyperemesis gravidarum. They also found that patients with hyperemesis gravidarum had significantly higher mean levels of free T_4, hCG, and total T_3, and a lower TSH level compared to control subjects. From these results, it was suggested that hyperemesis gravidarum may be caused by some not-yet-identified circulating stimulator. Abell and Riely,[22] suggested that there is a circulating hormone or hormone-like substance that may stimulate the thyroid gland and render it temporarily unresponsive to the control of the pituitary. This suggests that thyroid hormones are stimulated by something other than the TSH. By the time this substance subsides in later pregnancy, both the hyperemesis gravidarum and the hyperthyroidism resolve.

The serum leptin levels significantly differed ($p < 0.00$) between our three studied groups: the emesis and hyperemesis gravidarum groups had higher leptin levels than the healthy control group. However, the difference between women with emesis and hyperemesis gravidarum was not significant ($p > 0.05$). This agrees with Nurettin et al.[6] who found that their

group with hyperemesis gravidarum had significantly a higher serum leptin level ($p = 0.037$) than healthy pregnant women. But thyroid hormones and hCG levels in the two groups did not significantly differ.

In the hyperemesis gravidarum group in our study, only the serum leptin level positively correlated with the free T_3 level ($p < 0.05$). But three prospective cohort studies that compared the serum leptin levels between hyperemesis gravidarum patients and controls did not show a statistically significant difference.[23,24,25] Supporters of the leptin theory stated that this could be a false negative finding due to a negative energy balance in hyperemesis gravidarum patients, a dramatic decrease in leptin levels being observed in other condition with a negative energy balance, such as fasting.[26,27,28]

Our data show that patients with hyperemesis gravidarum had a significantly higher free T_4 level, but the level was within the reference range and the patients had no clinical manifestations of thyrotoxicosis. The group therefore had no underlying thyroid abnormality. It appears that neither thyroid hormones nor hCG contribute to the pathogenesis of hyperemesis gravidarum. Serum leptin, however, may play a role in the pathogenesis of hyperemesis gravidarum. Larger studies are needed to confirm this role.

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Clinical and Laboratory Studies

Assessment of Thyroid Function and Leptin Hormone in Women with Hyperemesis Gravidarum

Hussein Abdel Hai El Orabi,[1] Inas Mohamed Sabry,[1]
Ahmed Mohamed Awad Allah,[2] Alshymaa Alsayed Abd Alkhalek[1]

[1]Department of Internal Medicine; Endocrine Unit,
[2] Department of Gynecology and obstetric,
Ain Shams University; Cairo, Egypt

Corresponding author: Inas Mohamed Sabry Mohamed El Nabrawy MD,
Endocrine unit, Internal Medicine Department, Ain Shams University Hospitals,
Faculty of Medicine, Ain Shams University. Abbassia, Cairo, Egypt,
Address: 8 Nasr Street, 1st May Building, Nasr City, Cairo, Egypt.
Tel: +2 0101780318 Fax: +2 24845647 inassabry27@gmail.com nancy27eg@yahoo.com

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***Abstract.* Background.** Several studies have suggested that hyperemesis gravidarum in early pregnancy is related to women's levels of thyroid hormones, human chorionic gonadotropin (hCG), and serum leptin. To ascertain this relationship, we investigated 50 pregnant women in the first trimester. Twenty subjects had morning sickness, 20 had hyperemesis gravidarum, and 10 were healthy pregnant women who served as control subjects. **Methods.** The enzyme immunoassay method was used to measure all subjects' serum levels of T_3 (pg/mL), T_4 (ng/dL), TSH (μIU/mL), antithyroid peroxidase (anti-TPO) antibodies (IU/ml), and leptin (ng/mL). Serum β hCG was quantitatively assayed. **Results.** There was a statistically significant difference between the three studied groups as regards serum free T_4 ($p < 0.05$), but there was no difference as regards serum free T_3, TSH, anti-TPO, and serum β-hCG ($p > 0.05$). Serum leptin was significantly higher ($p < 0.001$) in the hyperemesis gravidarum and vomiting group compared to the healthy control group, with a non-significant difference between pregnant women with hyperemesis gravidrum and those with vomiting ($p > 0.05$). Correlation analysis showed that the only significant positive correlation was between serum T_3 and serum leptin ($p < 0.05$) in hyperemesis gravidarum. No significant correlation was found between β-hCG and thyroid hormones, antithyroid antibodies, and serum leptin in pregnant women with morning sickness and hyperemesis gravidarum ($p > 0.05$). **Conclusion.** Our results suggest that serum leptin levels are involved in the pathogenesis of hyperemesis gravidarum. No significant role was detected for thyroid hormones, serum β-hCG, or anti-TPO in patients with hyperemesis gravidarum.

Keywords • Hyperemesis gravidarum • hCG • Leptin • Pregnancy • T_3 • T_4 • Thyroid hormone

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INTRODUCTION

Hyperemesis gravidarum is a condition of intractable vomiting during pregnancy, leading to fluid, electrolyte and acid–base imbalance, nutritional deficiency, and weight loss often severe enough to require hospital admission.[1] Hyperemesis gravidarum is most prevalent during, but certainly not limited to, the first trimester of pregnancy when both the placenta and the corpus luteum are producing hormones and the body is adapting to the pregnancy state.[2]

Estimates of the incidence of hyperemesis gravidarum vary from 0.3 to 1.5% of all live births, with most authors reporting an incidence of 0.5%.[3,4] It is said to be higher in multiple pregnancies, hydatidiform mole, and other conditions associated with increased pregnancy hormone levels.[2]

Up to 80% of all pregnant women experience some form of nausea and vomiting during their pregnancies.[5] Because the great majority of pregnant women experience discomfort due to nausea and vomiting, a functional role of nausea and vomiting is often considered. Despite decades of research, the cause of these conditions remains unknown, and the relationship between nausea and vomiting during pregnancy and hyperemesis gravidarum is still unclear.[2] Many

etiopathogenic factors have been considered for hyperemesis gravidarum, including endocrine factors, hepatic dysfunction, changes in lipid metabolism, upper gastrointestinal system dysmotility, and psychological factors. However, no specific causative factor has been established.[6] Theories on how pregnancy hormones could cause hyperemesis gravidarum assert that patients who develop the condition may be exposed to higher levels of hormones during early pregnancy, especially progesterone and hCG. Also, irrespective of the gestational week, the rapid increase in the leptin concentrations in the first trimester may be a factor and also an early marker for hyperemesis gravidarum.[6]

Sometimes, thyroid hormone values deviate from the reference range, leading to a state referred to as gestational transient thyrotoxicosis (GTT). This has been observed in up to two thirds of women suffering from hyperemesis gravidarum.[7]

The etiology of transient hyperthyroidism of hyperemesis gravidarum is unclear. Some have argued that the hyperthyroidism is the cause of hyperemesis, whereas others have argued the reverse. The aim of this study was to evaluate the thyroid function, serum β-hCG, and serum leptin in women with hyperemesis gravidarum.

MATERIALS AND METHODS

A case-control study was conducted involving 50 pregnant women in their first trimester of pregnancy. The women were selected from the outpatient clinic of Maternity Clinic and the in-patient wards of the Hospital of Obstetric and Gynecology at Ain Shams University Hospitals. The patients were divided into three groups. The first group was patients with emesis (vomiting); the second group was patients with hyperemesis gravidarum [defined as persistent nausea and vomiting associated with ketosis and weight loss > 5% of pre-pregnancy weight];[8] and the third group was healthy pregnant women who served as controls.

All groups were adjusted for age, parity, and BMI. All included women were subjected to the following: full history taking, thorough clinical examination; measurement of serum TSH (μIU/mL) by electrochemiluminescence immunoassay (ECLIA); serum FT_3 (pg/mL), serum FT_4 (ng/dL), and anti-thyroid peroxidase (Anti-TPO)(IU/mL) by micro particle enzyme immunoassay (MEIA); serum β-human chorionic gonadotrophins (serum β-hCG) quantitatively by the Sandwich principle; serum leptin (ng/mL) by ELISA technique (normal value of serum leptin level is: < 50 ng/ml);[9] and blood urea (mg/dL), serum creatinine (mg/dL), serum sodium (mmol/l), serum potassium (mmol/L), and complete blood picture to detect the severity of emesis.

A blood sample of 15 cc was withdrawn from each subject and the blood sample was divided in the following way:

(a) 5 cc were used for a thyroid profile (TSH, FT_3, FT_4, and Anti-TPO);
(b) 5 cc were were collected and stored as serum in an aliquot at -20°C till time of assay for serum leptin.
(c) 5cc were used for blood electrolytes and urea, and serum creatinine and β-hCG (quantitative).

Also, ketones in a morning urine sample were measured with urine stripes.

Statistical Analysis. Data were collected, revised, verified, and then edited on a PC. Then data were analyzed statistically using SPSS statistical package, version 15. Data were expressed as mean ± SD for quantitative measures. The following tests were done:

1. The Student's-t test for independent variables and was used to assess significant differences between values in various groups of patients where appropriate.
2. ANOVA test was used for comparison between more than two independent groups as regard studied variables.
3. *Post hoc* test was used for comparison of quantitative variables.
4. Pearson correlation coefficient (r) was done for correlations between different studied parameters.
5. Sensitivity, specificity, and diagnostic accuracy at different cut-off levels and ROC-curves were analyzed.

The results were considered to be statistically significant at a p value of < 0.05, highly significant at p value of < 0.001, and insignificant at *a* p value of > 0.05.

RESULTS

As shown in Table 1, the only statistically significant differences between the three studied groups were in regard to the free T_4 and serum leptin ($p < 0.05$). The β-hCG level was higher in patients with hyperemesis gravidarum than in women with emesis and healthy controls, but the difference was not significant ($p > 0.05$). *Post hoc* testing for comparisons

of the three studied groups showed a significantly higher mean free T_4 level for group 2 compared to group 1 and group 3 ($p < 0.05$). But as shown in Table 2, the difference in the free T_4 level between group 1 and group 3 was not significant ($p > 0.05$). Also, the difference in leptin levels between the the emesis group and the hyperemesis gravidarum group was not significant ($p > 0.05$). However, the leptin levels in both the emesis group and hyperemesis gravidarum group were highly significantly higher than the level in the healthy control group ($p < 0.00$).

Table 1. The comparative data of all studied groups by ANOVA test.

Parameters	**Group (1)** (Pregnant with emesis)	**Group (2)** (Pregnant with hyperemesis gravidum)	**Group (3)** (Healthy pregnant control)	F	P	Sig
	N = 20	N = 20	N = 10			
FT_3 (pg/mL)	2.5 ± 0.5	2.6 ± 0.6	2.4 ± 0.5	0.6	> 0.05	NS
FT_4 (ng/dL)	***1 ± 0.1***	***1.3 ± 0.5***	***1 ± 0.2***	***4.1***	***< 0.05***	***S***
TSH(µIU/mL)	2.1 ± 1	1.4 ± 1.5	1.8 ± 0.9	1.9	> 0.05	NS
Anti-TPO (IU/mL)	6.4 ± 4.8	15.2 ± 29.2	5.1 ± 2.6	1.5	> 0.05	NS
β-hCG (mIU/mL)	79.7 ± 54.6	93.4 ± 57.8	69.5 ± 60.2	0.8	> 0.05	NS
Leptin (ng/mL)	**37.5 ± 28.8**	**43.6 ± 6.1**	***16.2 ± 9.2***	***9***	***< 0.00***	***HS***

NS=non significant, S= significant, HS= highly significant, N= number

Pearson correlation tests for the emesis group and the healthy control group, respectively, showed no significant correlation of serum leptin and serum β-hCG (r: 0.107) (r: 0.198), anti-TPO (r: 0.029) (r: -0.590), free T_4 (r: 0.145) (r: 0.287), and free T_3 (r: 0.322) (r: -0.374) ($p > 0.05$). In the hyperemesis gravidarum group, the serum leptin level was positively correlated with the free T_3 with an r value of 0.551 (Figure 1).

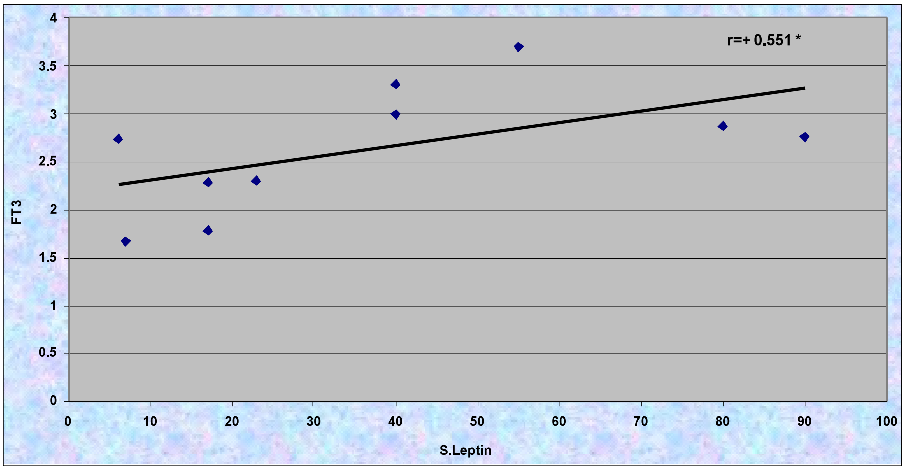

Figure 1. Correlation between serum leptin and FT3 in hyperemesis gravidarum.

In the healthy control group, the leptin level was significantly negatively correlated with the serum TSH ($r = -0.737$, $p < 0.05$). Also, in this group, the serum β-hCG level was positively correlated with the free T_3 level ($r = 0.755$, $p <0.05$).

In the emesis group and the hyperemesis gravidarum group, respectively, no correlation ($p > 0.05$) was found between the levels of serum β-hCG and anti-TPO (r: -0.146) (r: 0.021), serum leptin (r: 0.367((r: 0.107) [Figure 2], TSH (r: 0.344) (r:

-0.212), free T_4 (*r*: -0.248) (*r*: -0.312), and free T_3 (*r*: 0.050) (*r*: -0.359). Serum anti-TPO was positively correlated only with the free T_3 (*r*: 0.587) and the free T_4 (*r*: 0.938) in hyperemesis gravidarum group ($p < 0.01$) and the TSH (*r*: 0.447) in the emesis group ($p < 0.05$).

For the hyperemesis gravidarum group, the ROC curve detected the best cutoff point for the free T_4: 1.06 ng/dL, with a sensitivity = 80% and a specificity = 80 % and an area under the curve of 0.743 with a *p* value of < 0.004. But there was not a significant cut off point for serum leptin with a *p* value of > 0.05, a sensitivity = 60%, and a specificity = 53.3%.

Table 2. A multiple comparison study between all studied by *post hoc* test.

Parameters	Group (1) vs Group (2)			Group (1) vsGroup (3)			Group (2) vs Group (3)		
	LSD	P	Sig.	LSD	P	Sig.	LSD	P	Sig.
FT_3 (pg/mL)	-0.113	> 0.05	NS	0.111	> 0.05	NS	0.224	> 0.05	NS
FT_4 (ng/dL)	***-0.268***	***< 0.05***	***S***	-0.011	> 0.05	NS	***0.257***	***< 0.05***	***S***
TSH (µIU/mL)	0.719	> 0.05	NS	0.357	> 0.05	NS	-0.362	> 0.05	NS
Anti-TPO (IU/mL)	-8.82	> 0.05	NS	1.315	> 0.05	NS	10.135	> 0.05	NS
β-hCG (mIU/mL)	23.96	> 0.05	NS	13.765	> 0.05	NS	-10.195	> 0.05	NS
Leptin (ng/mL)	-6.100	> 0.05	NS	***-21.300***	***< 0.00***	***HS***	***-27.400***	***< 0.00***	***HS***

NS=non significant, S= significant, HS= highly significant, N= number

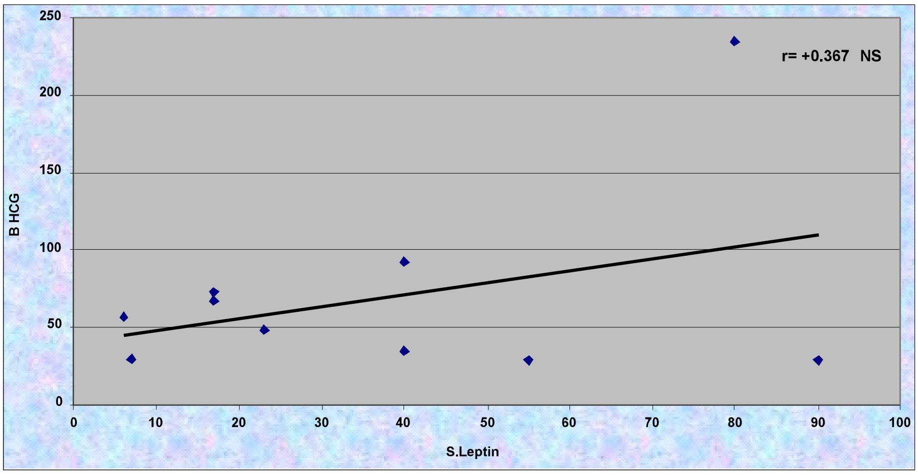

Figure 2. Non-significant correlation between serum leptin and β hCG in hyperemesis Gravidarum.

DISCUSSION

Hyperemesis gravidarum is defined as excessive vomiting during pregnancy, which may lead to sever outcomes including weight loss, dehydration, fasting acidosis, alkalosis due to hydrochloric acid loss, and hypokalemia.[10] Both the etiology and pathogenesis of hyperemesis gravidarum remain unknown.[2] The potential role of pregnancy-related hormones such as progesterone, estrogen, and hCG has been widely studied; however, various other hormones such as leptin, placental growth hormone, prolactin, thyroid hormone, and adrenal-cortical hormones have been implicated in the etiology of hyperemesis gravidarum.

The presence of an association between hyperemesis gravidarum and the rapid increase in leptin of placental origin, particularly in the first trimester, may be considered.[6] This study aimed to study thyroid hormones, serum β-hCG, anti-TPO, and serum leptin in women with hyperemesis gravidarum, and to detect any possible role of these parameters in the pathogenesis of hyperemesis gravidarum.

Our study revealed that there was no significant difference between the three studied groups as regards the free T_3, TSH, and anti-TPO ($p > 0.05$). Only the

free T_4 was significantly higher in the hyperemesis gravidarum group compared with the emesis group and the healthy control group ($p < 0.05$). However, the higher free T_4 was still within reference range.

The higher reference range free T_4 level in the hyperemesis gravidarum group can be explained by the characteristic pattern of serum free T_4 changes during normal pregnancy.

This pattern includes a slight and temporary rise in the free T_4 during the first trimester (due to the thyrotropic effect of hCG) and a tendency for serum free T_4 values to decrease progressively during later gestational stages.[11] But, although we found that the serum β-hCG level was higher in the hyperemesis gravidarum group than in the emesis group and the healthy control group, the level was not significantly different ($p > 0.05$).

This finding agrees with Al-Yatama et al.[12] They found that the serum free T_4 level was higher in hyperemesis gravidarum patients than in healthy controls ($p < 0.0001$), but no patients showed signs of thyrotoxicosis. We detected that the best significant cut off point of free T_4 for women with hyperemesis gravidarum was 1.06 ng/dL with a sensitivity = 80% and a specificity = 80% with a p value of < 0.004), which is still within the reference range for the free T_4. Panesar et al.[13] found by logistic regression analysis that the free thyroxine level was an independent variable. In addition, they found no significant difference between the free T_4 levels of healthy pregnant women and those with emesis ($p > 0.05$). Kimura et al.[14] found that serum free T_4 and free T_3 levels were higher in pregnant women with emesis and hyperemesis gravidarum ($p < 0.01$) and that the serum TSH was suppressed to less than 0.1mU/L in both groups. They also found, as we did in this study, that the serum β-hCG level did not significantly differ between the emesis group, hyperemesis gravidarum group, and the healthy control group. Also, Wilson et al.[15] reported no significant difference between the thyroid hormone and hCG levels of healthy controls and hyos peremesis gravidarum patients. In addition, Panesar et al.[13] observed that hGC is not independeetiology of hyperemesis gravidarum. In contrast, however, Al-Yatama et al.[12] reported that the total β-hCG level was significantly higher in hyperemesis gravidarum patients than in healthy control subjects.

Tan et al.[16] found that hyperemesis gravidarum patients were not clinically overtly thyrotoxic and thyroid antibodies were usually absent. But Taskin et al.[17] reported that the serum TSH and serum β-hCG levels were higher in women with hyperemesis gravidarum than in healthy pregnant women, while there was no significant difference between the groups as regards free T_3 and T_4 levels. However, Asakura et al.[18] found that free T_3 and free T_4 levels were significantly higher in hyperemesis gravidarum patients than in healthy controls; the levels were higher in the hyperemesis gravidarum patients with milder symptoms of morning sickness ($p < 0.05$). Also, Leylek et al.[19] found that the mean serum hCG, free T_3, and free T_4 levels were significantly higher in hyperemesis gravidarum patients than in healthy controls ($p < 0.05$), with a non-significant difference in serum TSH levels ($p > 0.05$). They also found that for hyperemesis gravidarum patients, the serum hCG significantly negatively correlated with the TSH and positively correlated with the free T_3 and free T_4. They found no relationship between β-hCG and thyroid function test levels in the control group ($p > 0.05$).

Our study did not show a significant correlation between serum β-hCG and serum TSH, free T_3, and free T_4 levels in hyperemesis gravidarum patients. In healthy controls, only the β-hCG level was positively correlated with the free T_3 ($r = 0.755$, $p < 0.05$). Tareen et al.,[20] demonstrated that serum T_4 and β-hCG were significantly increased in hyperemesis gravidarum, while the TSH significantly declined in the same group. They also found a direct relationship between the serum T_4 and β-hCG levels and an inverse relationship between the TSH and β-hCG levels in pregnant women with morning sickness.

Goodwin et al.[21] observed that the hCG level correlated directly with the free T_4 level and inversely with the TSH level ($p < 0.001$) in women with hyperemesis gravidarum. They also found that patients with hyperemesis gravidarum had significantly higher mean levels of free T_4, hCG, and total T_3, and a lower TSH level compared to control subjects. From these results, it was suggested that hyperemesis gravidarum may be caused by some not-yet-identified circulating stimulator. Abell and Riely,[22] suggested that there is a circulating hormone or hormone-like substance that may stimulate the thyroid gland and render it temporarily unresponsive to the control of the pituitary. This suggests that thyroid hormones are stimulated by something other than the TSH. By the time this substance subsides in later pregnancy, both the hyperemesis gravidarum and the hyperthyroidism resolve.

The serum leptin levels significantly differed ($p < 0.00$) between our three studied groups: the emesis and hyperemesis gravidarum groups had higher leptin levels than the healthy control group. However, the difference between women with emesis and hyperemesis gravidarum was not significant ($p > 0.05$). This agrees with Nurettin et al.[6] who found that their

group with hyperemesis gravidarum had significantly a higher serum leptin level ($p = 0.037$) than healthy pregnant women. But thyroid hormones and hCG levels in the two groups did not significantly differ.

In the hyperemesis gravidarum group in our study, only the serum leptin level positively correlated with the free T_3 level ($p < 0.05$). But three prospective cohort studies that compared the serum leptin levels between hyperemesis gravidarum patients and controls did not show a statistically significant difference.[23,24,25] Supporters of the leptin theory stated that this could be a false negative finding due to a negative energy balance in hyperemesis gravidarum patients, a dramatic decrease in leptin levels being observed in other condition with a negative energy balance, such as fasting.[26,27,28]

Our data show that patients with hyperemesis gravidarum had a significantly higher free T_4 level, but the level was within the reference range and the patients had no clinical manifestations of thyrotoxicosis. The group therefore had no underlying thyroid abnormality. It appears that neither thyroid hormones nor hCG contribute to the pathogenesis of hyperemesis gravidarum. Serum leptin, however, may play a role in the pathogenesis of hyperemesis gravidarum. Larger studies are needed to confirm this role.

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Dendritic Cell Expression of CD83 in Solitary Thyroid Nodules

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Fadila Gadalla,[1] Manal Abu Shady,[1] Ali El Shinawi,[1]
Sahar Saad El Din,[2] and Mohamed El-Shinawi[3]*

[1]Endocrinology unit, Internal Medicine department, Ain Shams University, Cairo, Egypt.
[2]Pathology department, Ain Shams University, Cairo, Egypt.
[3]General Surgery department, Ain Shams University, Cairo, Egypt.

Correspondence: Mohamed El-Shinawi, M.D.
Lecturer of General Surgery, Ain Shams University, Cairo 11566, Egypt.
Phone: (202)2670472 Fax: (202)26837673 mohamedshinawi@hotmail.com

Abstract. **Background**: Thyroid carcinoma typically presents as a dominant solitary thyroid nodule. Fine-needle aspiration biopsy (FNAB) is considered by most to be valuable in the evaluation of palpable thyroid nodules. At present, efforts are directed to find additional markers of malignancy that may prove to be useful adjuncts to FNAB. **Aim of the Study**: To establish the role of dendritic cell (DC) expression as a complementary marker to fine needle aspiration biopsy in the diagnosis of solitary thyroid nodules. **Study Design**: As CD83 is expressed on mature dendritic cells, CD83 + DC was studied by immunohistochemistry in 43 specimens from solitary thyroid nodules removed during surgery. They were compared to CD 83 + DC in surrounding tissue from the same patients. **Results**: CD83 + DC was significantly higher in papillary carcinoma (14.287±3.76) compared to normal tissue and to follicular carcinoma. DC expression was very low in medullary carcinoma (0.023±0.03) compared to normal tissue and to other cases of benign and malignant adenoma. The sensitivity of CD83 + DC was 85% and the specificity was 82%. **Conclusion**: CD83 + DC expression in papillary carcinoma may help in its differential diagnosis of follicular carcinoma from other papillary variants. In addition to fine needle aspiration biopsy, the very low DC expression in medullary carcinoma could help in the diagnosis of such cases. Dendritic cell expression potentially represents a new marker technique to improve the sensitivity and specificity in evaluating solitary thyroid nodules.

Keywords. CD83 • Dendritic cells • Papillary carcinoma • Thyroid nodules

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Fadila Gadalla,[1] Manal Abu Shady,[1] Ali El Shinawi,[1]
Sahar Saad El Din,[2] and Mohamed El-Shinawi[3]*

[1]Endocrinology unit, Internal Medicine department, Ain Shams University, Cairo, Egypt.
[2]Pathology department, Ain Shams University, Cairo, Egypt.
[3]General Surgery department, Ain Shams University, Cairo, Egypt.

Correspondence: Mohamed El-Shinawi, M.D.
Lecturer of General Surgery, Ain Shams University, Cairo 11566, Egypt.
Phone: (202)2670472 Fax: (202)26837673 mohamedshinawi@hotmail.com

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Keywords. CD83 • Dendritic cells • Papillary carcinoma • Thyroid nodules

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Introduction

Most thyroid nodules are harmless, do not cause symptoms, and do not require any treatment at all. However, approximately 5% of nodules are cancerous and therefore require attention. Cancer is less likely with multinodular goiter and more likely with single nodules.[1]

Dendritic cells (DCs) are unique antigen presenting cells (APCs) because they are the only ones that are able to induce primary immune responses, thus permitting establishment of immunological memory.[2] DCs are noted exclusively in neoplastic lesions, specifically at the periphery and within the tumor capsule. The specific distribution of DCs suggests a possible contribution to growth regulation of the thyroid neoplasm.[3]

Aim of the Work. The aim of our work is to establish the role of DC expression as a complementary marker to fine-needle aspiration biopsy (FNAB) in the diagnosis of solitary thyroid nodules. DC expression may become an ancillary tool in the diagnosis of thyroid carcinoma and in differentiating between adenoma and carcinoma.

Methods

Patients & Methods. We enrolled 43 patients (10 males and 33 females) from Ain Shams University Hospitals. The patients' ages ranged from 26-to-65. All human specimens were obtained with informed consent as approved by the Ain Shams University human research ethics committee. The patients were admitted for solitary thyroid nodules. They were subjected to surgeries that included total lobectomy and isthmectomy.

Pre-operative Assessment. A clinical examination of the thyroid nodule was performed. If a solitary thyroid nodule was suspicion to be malignant, it was excluded. Criteria for exclusion included hardness with limited mobility, lymphadenopathy, associated hoarseness, and dyspnea or dysphagia. The serum estimation of FT_3, FT_4, and ultrasensitive TSH were performed.

Radiological assessment included two procedures: an ultrasound of the thyroid gland using a real-time ultrasonographic scanner, and a thyroid scan using technetium 99m.

Intra-operative Specimens' Collection. Two samples from each patient was collected interoperatively using fine-needle aspiration biopsy. A sample was taken from the nodule and the other from neighboring thyroid tissue of the same lobe. Specimens were first preserved in formalin, then smeared onto slides, alcohol fixed, and then stained with haematoxlin and eosin. Specimens were evaluated by an expert pathologist.

The immunohistochemical staining SP method was performed to detect CD83. Formalin-fixed, paraffin-embedded thyroid specimens were washed three times in phosphate buffered saline. They were then treated with pepsin (0.5% in 0.01 N HCl) for 20 minutes at 37°C before staining for CD83. The specimens were then treated with normal goat serum for 20 minutes to block non-specific binding. The appropriate dilution (1:100) of mouse anti-human monoclonal antibody as primary antibody (PharMingen, San Diego, CA) was then added and incubated over night. The sections were then washed with phosphate buffered saline three times and reincubated with biotinylated goat anti-mouse immunoglobulin (1:200, DAKO, Denmark) at room temperature for 1 hour. After another wash with phosphate buffered saline, sections were soaked in alkaline phosphatese-conjugated streptavidin (DAKO), washed, and New Fuchshin (DAKO) were used as chromogen. Hematoxylin was used as a counter stain.

Expression of CD83 showing red granules was located on the membrane and/or in the cytoplasm of DCs; CD83-positive cells were counted over the whole specimens. The intensities of positive staining of S-100 was calculated by HpIAS1000 analysis system, shown as AGV (average grey value = |average positive grey value—average background grey value). The frequencies of CD83 positive cells were shown as the total numbers of cells/specimen.

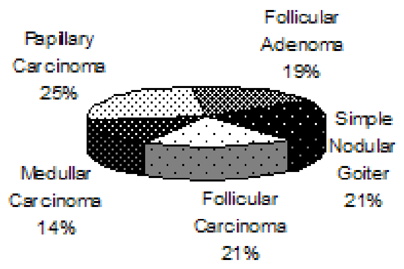
Statistical Analyses. Data were collected, revised, verified, and then edited on a personal computer. Data were then analyzed statistically using SPSS statistical package version 13. The following tests were performed:

1. $\bar{x}$ = mean.
2. SD = standard deviation.
3. T-test for independent samples.
4. Paired sample t test.
5. ANOVA = analysis of variance.
6. Post hoc test to detect LSD.
7. Pearson correlation.

Results

Figure 1 shows the percentage of pathological diagnosis of solitary thyroid nodules. A highly significant expression of mature dendritic cells CD83+ was found in papillary carcinoma as compared to normal thyroid ($p < 0.001$). There was also a significant difference between the CD83+ count in follicular carcinoma and follicular adenoma as compared to normal thyroid tissue ($p < 0.05$).

Figure 1. Percentages of pathological diagnoses of solitary thyroid nodules.



However, there was no significant difference ($p > 0.05$) between the CD83+ count in medullary carcinoma or simple nodular goiter of thyroid tissue and the CD83+ count in normal thyroid tissue taken from the same lobe (Table 1). A statistical significant difference ($p < 0.05$) was found between the CD83+ count in both follicular adenoma & carcinoma of thy-

Table 1. Expression of mature DC (CD83+) in solitary thyroid nodules and normal tissue.

Diagnosis	**Number of samples taken from Solitary nodule**		**Number of samples taken from Normal tissue**		***P* value**
	Total number = 43		**Total number = 43**		
	Number of patients	*DC (CD83+)*	*Number of patients*	*DC (CD83+)*	
Papillary carcinoma	11	14.2873 ± 3.7656	11	0.2545 ± 0.5732	< 0.001
Medullary carcinoma	6	0.0233 ± 0.03726	6	0.0033 ± 0.00745	> 0.05
Follicular carcinoma	9	5.2144 ± 1.7162	9	0.03667 ± 0.0771	<0.05
Follicular adenoma	8	5.2200 ± 1.8386	8	0.3125 ± 0.4190	<0.05
Simple nodular goiter	9	0.11555 ± 0.1372	9	0.11555 ± 0.1372	> 0.05

roid tissue and the CD83+ count in normal thyroid tissue of the same patients (Figure 2).

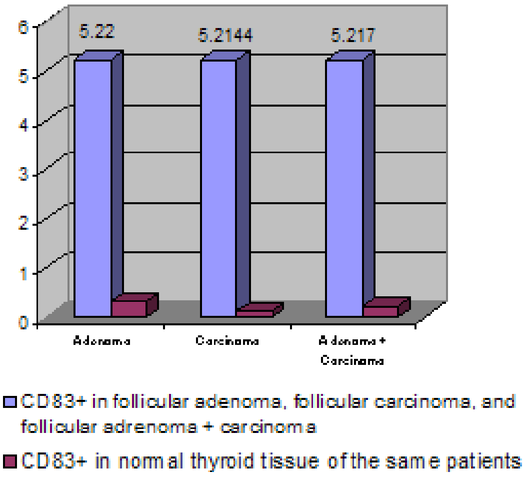
The mature DC expression in medullary carcinoma was very low and statistically significant compared to follicular carcinoma ($p < 0.05$). DC expression in medullary carcinoma was also significantly lower than that in papillary carcinomas ($p < 0.001$) (Table 2).

DC expression in papillary carcinoma was statistically higher ($P < 0.001$) than in follicular adenoma of thyroid tissue and simple nodular goiter of thyroid tissue (Table 3).

There was no significant correlation ($r = -0.146$) between different age groups and the CD83+ count. Also, in this study, no significance was found between DC expression and sex, family history, duration of the nodule, or the TSH level ($p > 0.05$)).

The sensitivity of dendritic cell expression for malignant thyroid carcinomas was 85%. The specificity was 82%.

Figure 2. (CD83+) Count in thyroid tissue follicular adenoma, follicular carcinoma, and follicular adrenoma + carcinoma compared to normal thyroid tissue.



Discussion

Thyroid cancer is a disease that may be fatal. This makes early diagnosis and treatment important in reducing mortality from the disease.

DCs have a central role in the initiation of primary immune responses. The cells are considered promising tools and targets for immunotherapy because of their capacity to stimulate naive T cells. DCs may play both prognostic and therapeutic roles in thyroid diseases.[4]

Histologically, normal thyroid tissue does not express DCs.[5] In this study, no mature DC expression was detected in normal thyroid tissue. In normal thyroid tissue, DCs are present as immature cells. They become mature only in response to a local inflammatory stimulus (the so-called danger signals), such as endotoxin (LPS), TNFa, and bacteria.[6]

It is clear from our study that mature dendritic cells were over expressed in papillary carcinoma ($\bar{x}$ of 14.2873) compared to normal thyroid tissue, other adenomas, and any other thyroid carcinoma. High expression of DCs in papillary carcinoma can help differentiate between it and other papillary variants; this can be useful when fine needle aspiration is suspicious. Dendritic cells, then, may be a crucial diagnostic tool for papillary carcinoma.

Table 2. Comparison between (CD83+) count in medullary carcinoma of thyroid tissue versus (CD83+) follicular carcinoma and papillary carcinoma of thyroid tissue.

DC(CD83+)	**In thyroid medullary carcinoma**		Mean difference	*P* value	Significance
	Mean ±SD	Number			
	0.0233 ± 0.03726	6			
In thyroid follicular carcinoma	5.2144 ± 1.7162	9	5.1911	< 0.05	Significant
In thyroid papillary carcinoma	14.2873 ± 3.7656	11	14.2639	< 0.01	Highly significant

The increased number of DCs in papillary carcinomas is possibly correlated with their good prognosis, irrespective of other morphological and clinical features.[7] Papillary cancers have also been shown to have a better cell-mediated immune response compared to controls and to follicular cancers. Thus the immune system, through the enhancement of inflammatory reactions induced by DCs, plays a major role in the clinical outcome of papillary thyroid cancer.[8]

There was no significant difference between mature DC expression in medullary carcinoma and normal thyroid tissue. This findings in our study agrees with the work of several other authors.[9,10,11]

Detecting DC expression can easily rule out or confirm medullary carcinoma. The reason is that compared to other carcinomas, DC expression in medullary carcinoma is significantly lower. DC immunotherapy has been introduced in the treatment of medullary thyroid carcinoma.[9]

In our study, positive risk factors such as a positive family history, age, gender, and the TSH level were not significantly related to DC expression. Our study results agree those of other studies concerning the lack of significant effect of positive risk factors in DC expression.[8,12] This indicates that DC expression is of significance in diagnosing papillary carcinoma irrespective of other factors.

It is established that FNAB is highly accurate in the diagnosis of thyroid malignancy. The sensitivity of the diagnostic procedure averages higher than 80% and specificity averages higher than 90%.[13] In our study, the sensitivity of the mature DC for malignant thyroid carcinomas was 85% and the specificity was 82%, for positive predictive value.

DC sensitivity for thyroid carcinoma will be 100% if medullary carcinoma is not included. The reason is that DC expression is positive for all thyroid carcinoma except for medullary carcinoma.

Conclusion

CD83+ DCs showed dense infiltration in papillary carcinoma. Its high density may be useful in the differential diagnosis of follicular carcinoma and other papillary variants. The very low DC expression in medullary carcinoma, in addition to fine needle aspiration biopsy, may help in the diagnosis of such cases. Dendritic cell expression potentially represents a new marker technique to improve sensitivity and specificity in evaluating solitary thyroid nodules.

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Fixed Dose Radioactive Iodine Therapy in Hyperthyroidism: Outcome and Factors Affecting it in a Region in South India

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Ajit S. Shinto, MBBS, DRM,DNB,PGDHA,
Leena Pachen, BSc, NMT,DNMT, and T.K. Sreekanth, BSc, MRT, DMRIT

Nuclear Medicine Department,
Amala Institute of Medical Sciences,
Amalanagar, Thrissur -555, Kerala, India

Correspondence: Dr. Ajit S Shinto, Nuclear Medicine Dept.,
Amala Institute of Medical Sciences, Amalanagar, Thrissur -555, Kerala, India
Office Tel: 04872304163 Personal cell: 09747714265 Fax: 04872304163
ajitshinto@gmail.com, ajitshinto@yahoo.com

Abstract. **Objective**: Radioactive iodine-131 (RAI or 131I) has been established as effective in the treatment of patients with various etiologies of hyperthyroidism. However, the short-term and long-term clinical outcome of patients receiving RAI differs in various studies. The aim of this study was to assess the clinical outcome one year after RAI therapy and identify factors associated with a good response. **Methods**: In this experimental study, 164 patients were included. They were randomly selected from patients referred to the Nuclear Medicine Department for Graves' disease, multinodular goiter, or toxic adenomas, which are indications for RAI therapy. The radioiodine dose was calculated based on the size of the thyroid gland by physical examination. Patients with normal thyroid glands were administered less than 10 mCi; patients with large thyroid glands or thyroid nodularity were administered a dose of greater than 10 mCi (approximately 15 mCi). Patients were monitored closely clinically and with blood investigations after treatment for one year. **Results**: Among 158 patients who completed follow up, 98.8% recovered and 1.2% remained thyrotoxic. Among patients who recovered, 74.2% became hypothyroid and 22.6% euthyroid. The incidence of hypothyroidism was 23% in first trimester, 43.7% in second trimester, 4.4% in third trimester, and 3.1% in forth trimester. **Conclusion**: In our study, a good result was seen in more patients than in other studies. The better outcome may be related to higher absorption of radioactive iodine in our region. The highest incidence of hypothyroidism was in the second trimester, so we recommend that patients should be carefully followed in this posttreatment period.

Keywords • Hyperthyroidism • Graves' disease • Radioiodine therapy • Outcome • Hypothyroidism

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Ajit S. Shinto, MBBS, DRM,DNB,PGDHA,
Leena Pachen, BSc, NMT,DNMT, and T.K. Sreekanth, BSc, MRT, DMRIT

Nuclear Medicine Department,
Amala Institute of Medical Sciences,
Amalanagar, Thrissur -555, Kerala, India

Correspondence: Dr. Ajit S Shinto, Nuclear Medicine Dept.,
Amala Institute of Medical Sciences, Amalanagar, Thrissur -555, Kerala, India
Office Tel: 04872304163 Personal cell: 09747714265 Fax: 04872304163
ajitshinto@gmail.com, ajitshinto@yahoo.com

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Keywords • Hyperthyroidism • Graves' disease • Radioiodine therapy • Outcome • Hypothyroidism

Introduction

Radioiodine therapy has enjoyed increasing popularity since its initial use in the 1960s for hyperthyroidism. Its popularity is based on its efficacy and low incidence of side effects.

Hyperthyroidism is a state of increased function of the thyroid gland leading usually to a clinical state of thyrotoxicosis. The most common cause of hyperthyroidism is Graves' disease, an autoimmune disease caused by an antibody (thyroid stimulating immunoglobulin) that is active against thyroid stimulating hormone receptors. Graves' disease accounts for 60%-to-80% of all cases of hyperthyroidism. Other common causes include toxic multinodular goiter and toxic adenomas.[1]

The main treatment options for persistent hyperthyroidism are antithyroid drugs, radioactive iodine (RAI), and surgery.[2,4,5] RAI-131, a radioactive isotope of iodine, is the treatment of choice for most patients with Graves' diseases and toxic nodular goiter. It is inexpensive, highly effective, easy to administer, tissue specific, and its safety has been proven in all age groups.[1]

Objectives of RAI Treatment. The primary goal of radioiodine therapy in Grave's disease is to cure the hyperthyroidism. It is controversial, however, whether radioiodine should be given in a dose sufficient to induce hypothyroidism or in a dose low dose in an attempt to provide the patient with a euthyroid state. Controversy exists also regarding the optimal dosing regimen of radioiodine to ablate the thyroid gland.

However, it is clear that most patients ultimately develop hypothyroidism after therapy. Administration of relatively low doses of RAI-131 are designed to avoid hypothyroidism and to restore euthyroidism. But the low doses may simply delay hypothyroidism or fail to cure the hyperthyroidism.[2,3] Most patients who become euthyroid soon after radioiodine therapy eventually develop hypothyroidism at a rate of approximately 5% per year.[4]

The aim of treatment is to destroy sufficient thyroid tissue to cure hyperthyroidism by rendering the patients euthyroid or hypothyroid in the long term. The treatment is highly effective with a cure rate approaching 100% after one or more treatments, depending on the dose administered and various other factors.[6]

Potential Complications of RAI Treatment. Some complications from RAI treatment have been reported. These include delayed control of symptoms; transient neck soreness; flushing and decreased taste; and posttreatment hypothyroidism in the majority of Graves' patients (82% after 25 years) regardless of dosage. In addition, radiation thyroiditis occurs in 1% of patients. Because Graves' ophthalmology may be exacerbated, pretreatment with antithyroid drugs is required for older or cardiac patients.[1]

Previously, there was concern that this form of therapy might also produce thyroid carcinoma, leukemia, or an increase in mutation rates. However, in more than seven decades in which RAI has been in use, no increased prevalence of thyroid or other carcinoma in treated patients has been noted.[7,8]

Table 1. Characteristics of study patients.

Variable		Number	Percentage
Sex	Female	113	71.5%
	Male	45	28.5%
Cause of hyperthyroidism	Graves' disease	134	84.8%
	Toxic multinodular goiter	13	8.2%
	Toxic adenoma	11	6.9%
Duration of pretreatment antithyroid drug therapy	Less than 1 year	38	24.1%
	More than 1 year	120	75.9%
Recurrences of disease before RAI	1 time	82	52%
	2 times	11	7%
	More than 2 times	19	1.2%
RAI dose	Less than 10 mCi	72	45.6%
	More than 10 mCi	86	54.4%

The most important side effect is hypothyroidism. Many treating physicians state that this is the inevitable outcome. Many reports have documented that the incidence of hypothyroidism is significant during the first year or two after treatment with RAI, and thereafter, the incidence continues to increase at a rate of approximately 5% per year. Studies have reported the incidence of post-RAI hypothyroidism at 5 years to be between 30% and 50%, depending on dosage and geographical factors. However, values as high as 70% have been reported.[9]

About 1% of patients who undergo RAI may experience radiation thyroiditis 5-to-10 days later. These patients usually experience pain over the thyroid area of the anterior neck. Some have thyroiditis-associated hyperthyroidism due to the release of stored thyroid hormone, and an occasional patient may progress to posttreatment thyroid storm.[10] Also, there has been reluctance to use RAI in women of childbearing years because of potential genetic damage in future offspring. Long-term follow up of patients has not validated this concern.[11,12]

There is concern, then, over the long-term effects of RAI treatment. The aim of this study was to address the concerns by assessing the outcome 1 year after patients had received RAI therapy.

Material and Methods

Our study had the approval of the institutional review board and ethics committee of our Institute.

The study was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all participating patients.

Patients who participated in the study were hyperthyroid patients referred to the Nuclear Medicine Department for RAI therapy for Graves' disease, multinodular goiter, or toxic adenoma. Among referred patients, 164 were randomly selected to take part in the study. (See Table 1 for characteristics of study patients.) Exclusion criteria were pregnancy, breast feeding, severe Graves' ophthalmopathy, and age under 20 years.

Iodine-containing medications were discontinued several weeks before RAI therapy and antithyroid-drugs were withdrawn at least 5 days before therapy. Most patients were put on pretreatment β-blockers that patients continued for approximately 2 weeks post therapy.

Doses of ^{131}I were calculated on the basis of the size of a patient's thyroid gland determined by physical examination. Patients with normal thyroid glands were given less than 10 mCi of ^{131}I; patients with large thyroid glands, and those with nodules as in toxic adenomas and toxic multinodular goiters, received more than 10 mCi. Most received approximately 15 mCi. Patients were advised to avoid physical contact and transfer of secretions to others for several days after treatment.

For one year after therapy, patients were monitored closely clinically and biochemically at frequent outpatient visits. After RAI therapy, a good result was considered either euthyroidism or hypothyroidism.

Statistical Analysis. For statistical analysis, categorical variables were compared with chi-square and the Fisher Exact test. Continuous variables that are normally distributed were expressed as mean ± SD. Statistical calculation was performed using a commercial computer package (Statistical Package for Social Sciences [SPSS], version 13.0) for Windows.

Results

At the beginning of the study, 164 subjects were selected but only 158 patients completed follow up. Of the 158 subjects, 134 (84.8%) had Graves' disease, 13 (8.2%) had multinodular goiter, and 12 (7.6%) had toxic adenomas. Before RAI therapy, 97.4% of the patients received antithyroid drugs. Of these patients, 75.5% were treated for more than one year. Before RAI therapy, 52% of the patients had one recurrence, 7% had two recurrences, and 1.2 % had three recurrences.

Among these patients, 98.8% recovered from hyperthyroidism and were either euthyroid or hypothyroid; 1.2% remained hyperthyroid. Among patients who recovered, 22.6% became euthyroid and 74.2% became hypothyroid.

The incidence of hypothyroidism was 23% in the first trimester, 43.7% in the second trimester, 4.4% in the third trimester, and 3.1% in the forth trimester (Table 3). A good result was obtained in 96.3% of Graves' disease patients and 100% of patients with toxic adenomas and multinodular goiters. Only 3.7% of Graves' disease patients did not achieve the desired result. Pleasant results were reported by 96.5% of women and 97.7% of men. Unpleasant results (hyperthyroidism) were reported by 3.5% of women and 2.3% of men.

No significant association was observed between sex and cure rate (P = 0.9). Significant pleasant results were observed in 93.2% of subject aged less than 35 years and 100% of subjects more than 35 years (P = 0.02). In subjects who received antithyroid medication, 96.7% obtained a good result and 3.2% obtained an unpleasant result, but this association was not significant (P = 0.9). A pleasant result was reported by 97.4% of patients who received antithyroid medications for less than one year, and 96.7% who received medication more than one year. This association also was not significant (P = 0.10). (Table 2). A good result was seen in 95.9% of patients who received less than 10 mCi RAI and in 97.7% of patients who received 15 mCi, but the correlation was not significant (P = 0.6) (Table 2). Also 100% of patients with normal thyroid size, 97.7% with moderate thyroid size (1.5-2 times more than normal), and 87% with large thyroid size (more than 2 times the normal size) obtained a good result (P = 0.2).

Discussion

RAI is widely used for the treatment of patients with thyroid disorders, particularly hyperthyroidism. However, the outcomes for patients who have received RAI have differed from study to study. In our study, a good result was seen in 96.3% of patients with Graves' disease and 100% of patients with toxic adenomas and multi nodular goiter. A second dose of RAI was needed by 15% of the patients, and a third dose for 5%. Through the year of patient observation, 74.2% of the patients became hypothyroid.

In our study, a good result was seen in more pa-

Table 2. Results according to different variables.

Variables		Good Result		Not Good Result	
		Number	Percentage	Number	Percentage
Sex	Female	109	96.5%	4	3.5%
	Male	44	97.7%	1	2.3%
Age	Less than 35 years	69	93.2%	5	6.8%
	More than 35 years	84	100%	—	—
Pretreatment antithyroid drug duration	Less than 1 year	37	97.4%	1	2.8%
	More than 1 year	116	96.7%	4	3.3%
RAI dose	Less than 10 mCi	69	95.8%	3	4.2%
	More than 10 mCi	84	97.7%	2	2.3%

tients than other studies. This positive result may have been due to a higher absorption of radioactive iodine in our region. Taylor et al studied 225 patients who were treated with 555 MBq (15 mCi) RAI for hyperthyroidism to ablate the thyroid and induce early hypothyroidism. With this fixed dose regimen, only 5.6% failed to become euthyroid within one year of treatment. Ten patients (4.4%) required a second dose of 555 MBq ^{131}I since they were still hyperthyroid 1 year after RAI treatment; 3 of these patients required a third dose.[13]

Our patients received 10 mCi or more RAI on the basis of the size of the thyroid gland determined by physical examination. The optimal method for determining the appropriate iodine-131 treatment dose remains controversial. Techniques have varied from fixed doses[14-16] to more elaborate calculations based upon gland size (estimated either by palpation or imaging), iodine uptake, and sometimes from iodine turnover.[17-20]

Leslie et al. studied 88 patients with Graves' hyperthyroidism who had not previously been treated with radioactive iodine. The patients were randomized to one of four dose-calculation methods: low-fixed, 235 MBq; high-fixed, 350 MBq; low-adjusted, 2.96 MBq (80-Ci)/g thyroid adjusted for 24 h RAI uptake; and high-adjusted, 4.44 MBq (120-Ci)/g thyroid adjusted for 24-hour RAI uptake. Subjects were followed for a mean of 63 months to assess clinical outcomes. Mean treatment doses were similar in the different outcome groups. Leslie et al. could not demonstrate any advantage to using an adjusted dose method. Survival analysis did not demonstrate any difference in the time to outcome between the fixed and adjusted dose methods.[21]

Mazzaferri et al., in their study on 813 hyperthyroid patients, divided them into two groups. The first group received 185 MBq, and the second group received 370 MBq. At the end of their study period, the first group had an incidence of hypothyroidism of 41.3%, and the second group had an incidence of 60.8%.[22]

Most dosimetric methods have the benefit of including a measure of thyroid size in their formulas, thereby administering a dose of RAI proportional to size of the gland. This theoretically increases the probability of cure. In addition, the use of isotope uptake measurements, as part of the dose calculation protocol, can confirm the absence of thyroiditis and identify patients with extremes of isotope uptake or turnover, which may predict failure of RAI treatment.[23] Despite these potential benefits of calculated doses, several studies have failed to demonstrate improvements in cure rate over fixed doses.[24-26] Furthermore, there is little evidence that using a calculated dose has any advantage over a fixed-dose regimen in preventing hypothyroidism.[27] Because of this, many centers use a single fixed dose.[28]

We administrated RAI of approximately 15 mCi to patients with toxic mulitinodular goiters and toxic adenomas. Opinions also vary about the need for larger doses of RAI in toxic nodular goiter, as compared with Graves' disease.[29,30] Patients with hyperthyroidism from toxic nodular goiters are perceived to be relatively radio-resistant compared to patients with Graves' disease,[29] although evidence is conflicting. Consistent with this perception, researchers report studies in which they administered relative large but varied doses of RAI (555–1850 MBq) to patients with toxic nodular goiters.[31,32]

In our study, results show no difference in the cure rate between the two different doses of RAI.

However, the size of the gland was different in the two groups and hence the results cannot be universally applied. Allahabadia et al. reported that in patients given a single dose of 370 megabequerels , a higher cure rate (84.6% vs. 66.6%) was achieved than when 185 megabequerels were administered. But at one year follow up, patients who received the larger dose had a higher incidence of hypothyroidism (60.8% vs. 41.3%).[33]

Table 3. Incidence of hypothyroidism after RAI according to time.

Time	Number	Percentage
First trimester	38	23%
Second trimester	69	43.7%
Third trimester	6	4.4%
Fourth Trimester	5	3.1%

In the Allahabadia et al. study, age was associated with treatment outcome: younger patients (< 40 years) had a lower cure rate (68.9% vs 79.3%) than patients over 40 years old.[33] In our study, we found a cure rate of 93.2% in patients below 35 and 100% in patients above 35. Compared to the Allahabadia et al. study, a higher percentage of younger patients had a good outcome. According to our results, then, RAI can be offered to younger patients.

We did not observe a significant association between cure rate and sex. This result is consistent with the outcome of many other studies that did not show gender to be a significant prognostic factor in patients' responses to RAI treatment. In contrast, Allahabadia et al. found that males had a significantly lower cure rate than females after one dose of RAI.[33]

Several studies have demonstrated that patients with larger volume thyroid glands are more likely to fail to respond to a single dose of RAI.[33] In our study, the cure rate was lower for patients with smaller thyroid glands, but no significant correlation could be drawn.

Our findings show no significant correlation between pretreatment with antithyroid-drugs and duration of thyroid gland pathology and cure rate. Many studies have shown a reduction in the response rate to RAI[34,35] if patients have received pretreatment with thyroid drugs. Other studies, however, have shown either no effect[36] or an effect confined to propylthiouracil.[37]

For example, Alexander et al. treated 261 patients with hyperthyroidism caused by Graves' disease with ^{131}I [mean dose, 14.6 mCi (540 MBq)]. Patients pretreated with antithyroid medication for greater than 4 months were at higher risk for treatment failure.[38] Some other studies also demonstrated that antithyroid-drug pretreatment may cause an exacerbation or recurrence of hyperthyroidism.[39,40]

On the other hand, Braga and Andrade et al. demonstrated that methimazole pretreatment has no effect on the final result, the time required for cure, or the 1-year success rate of ^{131}I therapy.[41,42] In contrast, Ahmad et al. demonstrated that the frequency of hypothyroidism was lower in patients treated with antithyroid drugs prior to RAI compared with patients who did not received antithyroid drugs.

Ahmed et al. studied risk factors that allow estimates of the probability of developing hypothyroidism following radioactive iodine treatment.[43] Hypothyroidism was reported to occur from 2 months to 20-to-30 years after RAI therapy. As significant independent risk factors, they identified Graves' disease, the presence of thyroid autoantibodies, no antithyroid treatment given prior to RAI, a nonpalpable goiter, and a high RAI dose. The researchers reported that in the absence of all risk factors, the probability of developing hypothyroidism is 11.9%. In the presence of all risk factors, the probability increases linearly to 96.4%.

In our study, hypothyroidism was seen in 74.2% of subjects, mostly in the second trimester post therapy. Similarly, in a study by Nebesio et al., hypothyroidism was observed in 75% patients 40-to-90 days after RAI.[44] By comparison, Ahmad et al. [43] reported that the cumulative incidence of hypothyroidism following RAI treatment was 38.2% after 6 months. The incidence increased to 55.8% after 1 year and to 86.1% at 10 years.[43] In Kendall-Taylor et al. study the modal time to hypothyroidism was three months, and 64% of patients were hypothyroid at one year.[13]

These data suggest that our patients' cure rate was higher than in other studies. The high rate may have been contributed to by two factors: our low sample size and higher RAI absorption in our patients due to regional iodine insufficiency compared to iodine sufficiency in regions where other studies were conducted.

No significant association was observed between cure rate and gender, antithyroid-drug pretreatment, duration of antithyroid-drug pretreatment, or RAI dose. According to our results, the incidence of hypothyroidism was highest in the second trimester following RAI therapy. Because of this, we recommend that patients be carefully followed in this period.

Study Limitations

A limitation of our study is the sample size which was relatively small. Because of this, our negative results may reflect a lack of power. Further studies to confirm or refute our results with longer follow up times and larger sample sizes are suggested.

Also the hypothesis that the better cure rate was due to higher iodine absorption is not verified due to the lack of an iodine uptake probe. However, an association between gamma-camera calculated thyroid uptake and cure rate is to be studied to determine whether there is a relationship between a higher cure rate and higher ^{131}I absorption.

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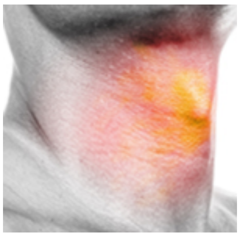

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Low Dose I-131 Therapy in Differentiated Thyroid Cancer: An Initial Experience

(Full Text Free in pdf format)

Ajit S. Shinto, MBBS, DRM, DNB, MNAMS, PGDHA; T.B Culas, MS;
M.V. Suresh, MS; J. Mathew, MS; Ajay Kumar, MCh; M.L. Dathan, MS,FRCS;
Sree Kumar Pillai, MCh; and C.D. Joseph, MD,DABR

Nuclear Medicine Department,
Amala Institute of Medical Sciences,
Amalanagar, Thrissur -555, Kerala, India

Correspondence: Dr. Ajit S Shinto, Nuclear Medicine Dept.,
Amala Institute of Medical Sciences, Amalanagar, Thrissur -555, Kerala, India
Office Tel: 04872304163 Personal cell: 09747714265 Fax: 04872304163
ajitshinto@gmail.com, ajitshinto@yahoo.com

Abstract. **Objective**: Since the 1970s, low dose radioactive iodine-131 (RAI or I-131) has been widely reported in the treatment of patients with differentiated thyroid cancer (DTC). However, the clinical outcomes, dosage of I-131, and criteria for successful ablation differ in the various studies. The aim of this study was to assess the clinical outcome 18 months after RAI therapy in selected DTC patients, and to identify factors associated with a good response. **Methods**: In this experimental study, 105 subjects were randomly selected from patients with DTC referred to the Nuclear Medicine Department between December 2008 and April 2010 and who had indications for RAI therapy. Patients were randomly divided into 3 groups to receive an empiric low-dose therapy of either 30, 40, or 50 mCi of I-131. For 18 months after treatment, at 6-month intervals, patients were monitored closely clinically, with serum thyroglobulin assays, and with I-131 whole-body scans. **Results**: Among 105 patients who completed followup, 86 % were successfully ablated with a single low dose of I-131. There was no statistically-significant difference in ablation rates between the subgroups that receive 30,40, or 50 mCi of I-131. The cumulative ablation rate was 99% in patients after the second dose of low dose therapy. **Conclusion**: If appropriate selection criteria are used in DTC, successful remnant ablation can be achieved with low doses of I-131 in the range of 30-to-50 mCi. No significant differences were found in results achieved with 30, 40, or 50 mCi of I-131I. As the majority of the DTC patients fall within the inclusion criteria of this study, they can be treated on an ambulatory basis with associated low cost, convenience, and a low whole-body radiation-absorbed dose of I-131.

Keywords • Hyperthyroidism • Graves' disease • Radioiodine therapy • Outcome • Hypothyroidism

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Low Dose ^{131}I Therapy in Differentiated Thyroid Cancer: An Initial Experience

Ajit S. Shinto, MBBS, DRM, DNB, MNAMS, PGDHA; T.B Culas, MS;
M.V. Suresh, MS; J. Mathew, MS; Ajay Kumar, MCh; M.L. Dathan, MS,FRCS;
Sree Kumar Pillai, MCh; and C.D. Joseph, MD,DABR

Nuclear Medicine Department,
Amala Institute of Medical Sciences,
Amalanagar, Thrissur -555, Kerala, India

Correspondence: Dr. Ajit S Shinto, Nuclear Medicine Dept.,
Amala Institute of Medical Sciences, Amalanagar, Thrissur -555, Kerala, India
Office Tel: 04872304163 Personal cell: 09747714265 Fax: 04872304163
ajitshinto@gmail.com, ajitshinto@yahoo.com

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Abstract. **Objective**: Since the 1970s, low dose radioactive iodine-131 (RAI or ^{131}I) has been widely reported in the treatment of patients with differentiated thyroid cancer (DTC). However, the clinical outcomes, dosage of ^{131}I, and criteria for successful ablation differ in the various studies. The aim of this study was to assess the clinical outcome 18 months after RAI therapy in selected DTC patients, and to identify factors associated with a good response. **Methods**: In this experimental study, 105 subjects were randomly selected from patients with DTC referred to the Nuclear Medicine Department between December 2008 and April 2010 and who had indications for RAI therapy. Patients were randomly divided into 3 groups to receive an empiric low-dose therapy of either 30, 40, or 50 mCi of ^{131}I. For 18 months after treatment, at 6-month intervals, patients were monitored closely clinically, with serum thyroglobulin assays, and with ^{131}I whole-body scans. **Results**: Among 105 patients who completed followup, 86 % were successfully ablated with a single low dose of ^{131}I. There was no statistically-significant difference in ablation rates between the subgroups that receive 30,40, or 50 mCi of ^{131}I. The cumulative ablation rate was 99% in patients after the second dose of low dose therapy. **Conclusion**: If appropriate selection criteria are used in DTC, successful remnant ablation can be achieved with low doses of ^{131}I in the range of 30-to-50 mCi. No significant differences were found in results achieved with 30, 40, or 50 mCi of ^{131}I. As the majority of the DTC patients fall within the inclusion criteria of this study, they can be treated on an ambulatory basis with associated low cost, convenience, and a low whole-body radiation-absorbed dose of ^{131}I.

Keywords • Hyperthyroidism • Graves' disease • Radioiodine therapy • Outcome • Hypothyroidism

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Introduction

The current accepted therapy for differentiated thyroid carcinoma is total thyroidectomy or near-total thyroidectomy followed by radioiodine (^{131}I) ablation of residual thyroid tissue, termed "remnant ablation." There are several arguments and compelling reasons for remnant ablation in cases of differentiated thyroid cancer, and these have been dealt with in detail elsewhere.[21]

Although ^{131}I has been used for many years to ablate thyroid remnants following thyroid surgery, a single optimal ablation strategy is still not established. Varied reports on the amount of ^{131}I required to achieve successful ablation, criteria for successful ablation, and long-term disease-free survival and recurrence rates show a considerable range.[1,2]

In this context, multiple studies have established the adequacy of low dose ^{131}I in successfully ablating remanant thyroid in selected patients with a dose as small as 30-to-50 mCi.[3-11] The proposed advantages of the dosage range are lower cost; minimizing whole-body radiation exposure, and hence lowering the potential risk of leukaemogenesis; and the practical advantage of economy and convenience of outpatient treatment in many countries. Thus, the objective of the present study was to determine successful ablation rates in selected differentiated thyroid cancer patients with small single doses of ^{131}I.

Patients and Methods

Study Design. One hundred and five patients with well-differentiated thyroid cancer were selected as study subjects. The patients had received 1110-to-1850 MBq of ^{131}I for ablation of residual functioning thyroid tissue 1.5 months (median) after total or subtotal thyroidectomies performed between December 2008 and April 2010.

Inclusion Criteria. To be included in the study, patients were required to have disease that was limited to the thyroid bed, confirmed by clinical, radiological, peroperative, and postsurgical ^{131}I scintigraphic examination. Patients were also required to have no evidence of extrathyroid or distant metastases at the time of presentation. The amount of thyroid tissue left behind or the completeness of surgery did not affect the dose of ^{131}I given.

Exclusion Criteria. Patients with inadequate surgery were excluded. Inadequate surgery was qualitatively defined as significant bilateral thyroid uptake on the first ^{131}I scan or > 5 cm initial tumour size on histological examination.

Patients were also excluded if they had any of a number of extrathyroid diseases: nodal or distant metastases, adverse histopathology-like Hürthle cell carcinoma, poorly differentiated carcinoma, insular carcinoma, medullary thyroid carcinoma, and the aggressive variant of papillary carcinoma. Moreover, if the first postoperative thyroid scan of a patient who had had a total thyroidectomy showed a substantial uptake in the thyroid bed, he or she was reclassified as having had a subtotal thyroidectomy and was excluded from the study.

The median duration of the illness before surgery was 29 months; the range was 1–to-370 months). Mean tumor size was 3.8 ± 1.2 cm. The large tumor size was probably due to late referral to surgery. The initial surgical intervention was not uniform due to different surgical units operating upon the patients. The surgical procedure followed was near total thyroidectomy or total thyroidectomy in all of the patients. The histopathological diagnosis was established in all patients and classified according to the World Health Organization criteria.[12] Eighty four patients (80%) had papillary thyroid carcinoma, and 21 (20 %) had follicular thyroid carcinoma.

The interval between surgery and referral to the Department of Nuclear Medicine for remnant ablation ranged from 2 days to 2 months with a median value of 1 month. Postsurgical whole body scans were performed with 0.8-to-1.0 mCi of ^{131}I after keeping patients off L-thyroxin for 4–to-6 weeks. Preablation serum TSH values among patients ranged between 25 and 98 µIU/ml (mean = 54 ± 14). Although patients were not prescribed special low-iodine diets, they were advised not to take in foods or drugs known to be rich in iodine or to undergo contrast CT scans. The patients were given oral ^{131}I as NaI therapeutic capsules with dosages of 30-to-50 mCi. Informed consents were obtained from all adult patients before administration of ^{131}I.

After ^{131}I therapy, all patients underwent post-therapy whole body scans. The purpose was to look for any nodal or distant metastases missed on the previous postsurgical low-dose whole body scans.

The patients were then advised to take levothyroxine (2 µg/kg body weight) daily on an empty stomach as suppressive therapy. This was continued until 6 months later when diagnostic ^{131}I whole body studies were repeated. The preparation for the 6-month post-therapy evaluation was similar to that for the preablation scan. No recombinant human TSH was used in this study. All patients were prepared by conventional methods with serum TSH levels more than 30 µIU/mL.

The repeated diagnostic studies consisted of 2–to-3 mCi ^{131}I whole body scans and serum thyroglobulin assays. The criteria for successful ablation were as follows: a negative ^{131}I whole body scan and thyroglobulin less than or equal to 1 ng/mL. If patients met these criteria, they were classified as having achieved complete remnant ablation. If, however, after the first posttherapeutic evaluation, a patient did not meet the criteria for complete thyroid ablation, then additional ^{131}I treatment (30–to-50 mCi) was administered. Repeat ^{131}I doses were administered until thyroid ablation was achieved. Afterward, annual check-ups were planned for thyroglobulin estimation.

Results

The mean age of the patients was 39 ± 12.7 years with a female-to-male ratio of 2.6. The mean tumor size was 3.8 ± 1.2 cm. Successful remnant ablation was achieved with one dose of ^{131}I in 90 (86%) of the 105 patients. Their mean thyroglobulin level was 0.5 ± 0.1 ng/mL. The remaining patients showed partial ablation, objectively assessed by reductions in scan uptake intensity or number of foci and low thyroglobulin levels.

There was no statistically significant difference in the first-dose outcome (remnant ablation) between patients receiving 30 mCi of ^{131}I (44% of patients), 40 mCi(32% of patients), or 50 mCi (24% of patients). Remnant ablation rates were almost identical between patients administered 30, 40 and 50 mCi of ^{131}I (84%, 92%, and 88% ablation rates, respectively). No statistically significant associations were found between successful ablation rates and mean group differences in tumor size and other demographical factors.

Two doses of ^{131}I were administered to 15 patients. The rate of successful remnant ablation after the second dose of ^{131}I was 99%. All patients were followed up for 18 months. So far, no cases of local recurrence or nodal or distant metastasis have been observed in the study cohort. Also, no deaths have occurred.

Table I. Demographic data, clinical profiles, and treatment outcomes of all patients.

Parameters	**Total**	**30 mCi**	**40 mCi**	**50 mCi**
Age (years)[1]	39 ± 12.7	37.5±11.6	41±13.6	39.9 ± 13.7
Sex (female:male)	2.6:1	2.7:1	2.4:1	3:1
Median duration of illness (months)	18	20	18	16
Tumor size (cm)[1]	3.8 ± 1.2	4.5 ± 1.6	3.6 ± 1.7	5.1 ± 2.1
Surgery NTT[2]	105	46	34	25
Histopathology[3]				
Papillary	84	36	22	18
Follicular	21	10	12	7
Successful ablation1(% of patients)	90 (86%)	39 (84%)	31(92%)	22 (88%)
Patients requiring second dose	15	7	3	3
Cumulative ablation after 2nd dose 1 (% of patients)	104 (99%)	45 (97.8%)	34 (100%)	25 (100%)

[1] Age and tumor size are given in terms of mean ± SD; duration of illness is given as median

[2] Near total thyroidectomy

[3] Number of patients.

Discussion

There are multiple reports attesting to the efficacy of low-dose (30-to-50 mCi) ablative therapy for thyroid remnants since 1970's. One of the first reports of such therapy emphasized its effectiveness relative to the standard higher dose of ^{131}I.[3]

The initial belief and practice was that a higher dose of ^{131}I should be administered as it more effectively achieved complete ablation with a single administration. Proponents of this higher-dose ^{131}I remnant ablation argued that administering larger doses also ablated possible micrometastatic deposits. Their corollary argument was that lower doses were less effective in ablating the micrometastases not visualized in a posttherapy whole body scans, and thereby possibly led to a higher recurrence rate and metastases.[10] However, Mazzaferri and Kloos[11] addressed these arguments and found no difference in 30-year recurrence rates (4% and 6%, respectively; $P = 0.1$) between low-dose (29–to-50 mCi) and high-dose (51–to-200 mCi) ^{131}I remnant ablation groups.

The present study provides additional data on the effectiveness of the 30-to-50 mCi dose range. Our results show that a single 30-to-50 mCi dose resulted in successful ablation in 86% of the patients at 1 year post iodine therapy. A single low dose of ^{131}I was sufficient in the majority of the cases to render the followup ^{131}I scan negative and to provide considerably lower thyroglobulin levels.

A negative ^{131}I scan and low thyroglobulin level would be reasonable criteria of successful therapy if the only concern were the detection of iodine-retaining malignant thyroid tissue. It is likely, however, that more complete ablation of non-neoplastic thyroid tissue is necessary to afford the advantages of decreased recurrences of thyroid carcinoma and increased patient survival.[11,13-17]

Our experience in following patients with minimally positive scans indicates that some may become negative without further ^{131}I therapy. Nevertheless, since 30 mCi is the largest dose usually approved for outpatients in many countries, it may be reasonable to combine the therapeutic and diagnostic efficacy of

30-mCi doses for ablation of thyroid remnants. The benefits of low-dose therapy, in addition to economy and convenience, relate primarily to a reduced total radiation exposure to extrathyroidal target organs. This reduction pertains mainly to the 86% of patients in whom ablation is achieved with a single 30-mCi dose.

However, repeated low-dose exposures, which allow for tissue repair mechanisms to proceed in the interim, may cause less biologic damage than the same total dose delivered at one time. Therefore, even patients requiring two such doses may benefit. The risk of leukemia and ovarian injury after thyroid ablation doses under 150 mCi is unknown, but is probably very small. Pochin[18] reported four cases of leukemia in 140 patients who received an average total dose of 735 mCi. Pochin's leukemia cases received 1130-to-1715 mCi, and other cases gathered from the literature by Brincker et al.[19] received 261-too-1600 mCi. Regarding ovarian injury, Sarkar et al.[20] followed 33 young patients for an average of 19 years following treatment with 80-to-691mCi (mean of 196 mCi). The investigators found no evidence of radiation-induced problems in fertility or in the offspring of the young adults.

Despite the lack of evidence of injury with doses below 150 mCi, it seems prudent to mitigate radiation exposure by using the minimal effective dose to achieve the desired purpose. But disadvantages of low-dose therapy have been reported. First, about half of the patients require more treatment, resulting in more periods of T_3 withdrawal and hypothyroidism, and a longer time required to achieve ablation. Second, unrecognized metastases may be in adequately irradiated. This may reduce the function of the neoplastic cells but not their growth. A long-term, prospective randomized controlled study is needed to evaluate the importance of these factors in the efficacy of low-dose ablation therapy.

Our results suggest that use of a single low dose in the proper clinical setting results in successful ablation in a majority of patients. Thus, single low-dose therapy is a reasonable approach to ablation therapy, especially in young subjects with well-differentiated thyroid cancer. Our results also suggest that a minimally positive whole body scan 6 months after a therapeutic dose of ^{131}I is an indication for further follow-up rather than immediate further treatment.

Conclusion

If appropriate selection criteria are used in differentiated thyroid cancer, successful remnant ablation can be achieved with low doses, in the range of 30-to-50 mCi. No significant differences were found in results achieved with 30, 40, or 50 mCi of ^{131}I. The majority of differentiated thyroid cancer patients fall within the inclusion criteria of this study. Because of this, patients can be treated on an ambulatory basis with associated low cost, convenience, and low whole-body radiation-absorbed doses.

Limitations of Study

Patients with incomplete initial surgery, poorly differentiated tumors, aggressive histology, or metastatic disease were not included in this study. Results of this study therefore cannot be extrapolated to this population of patients, and high-dose ablation therapy may be preferable for them.

In addition, treatment outcomes and recurrence rates among patients who met the inclusion criteria for this study would best be assessed through long-term followup.

Disclosure

No financial support or grants were availed to conduct or complete the study.

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Prevalence of Antithyroid Antibodies in Histologically Proven Autoimmune Thyroid Diseases and Correlation with Thyroid Dysfunction in South India

(Full Text Free in pdf format)

Ajit S. Shinto, MBBS, DRM,DNB,PGDHA, Leena Pachen, BSc, NMT,DNMT,
Sreekanth T.K., BSc, MRT, DMRIT, Deepu George, MD

Nuclear Medicine Department,
Amala Institute of Medical Sciences,
Amalanagar, Thrissur -555, Kerala, India

Correspondence: Dr. Ajit S Shinto, Nuclear Medicine Dept.,
Amala Institute of Medical Sciences, Amalanagar, Thrissur -555, Kerala, India
Office Tel: 04872304163 Personal cell: 09747714265 Fax: 04872304163
ajitshinto@gmail.com, ajitshinto@yahoo.com

***Abstract*. Objective**: The clinical diagnosis of autoimmune thyroid diseases (AITD) is usually confirmed by detection of various antibodies in the patient's blood or by histopathological evaluation. In this study, we evaluated the prevalence of serum antibodies in histopathologically proven AITD and assessed the correlation between antibodies and thyroid dysfunction. **Methods**: 100 consecutive patients with a histological diagnosis of AITD were included in the study and underwent detailed clinical examination and testing for thyroid function, thyroid antibodies, thyroid ultrasound scan, and thyroid gland fine-needle aspiration cytology. **Results**: Thyroid peroxidase antibodies (TPO Ab) tested positive in 89% of patients and negative in 11%. Antithyroglobulin antibody (ATG Ab) estimation was positive in 64 % of patients and negative in 36%. By thyroid function testing and serum antibody evaluation, of the 89 TPO-positive patients, 60.7% were hypothyroid, 6.7% hyperthyroid, and 32.6% euthyroid. Among euthyroid patients, 90% were TPO-Ab negative. In 64 ATG Ab-positive patients, 53.1% patients were hypothyroid, 4.7% hyperthyroid, and 42.2% euthyroid. But in the 36 ATG Ab-negative patients, 58.3% were hypothyroid. At the time of the first clinic visit, 55% of patients were hypothyroid, 6% hyperthyroid, and 39% euthyroid. **Conclusion**: In our study, TPO Ab was more sensitive than ATG Ab in predicting hypothyroidism. Similarly, TPO Ab was more sensitive than ATG Ab in autoimmune thyroiditis (98.1% vs 61.8%, p value < 0.005). Hypothyroidism was the most frequent thyroid dysfunction in patients with positive TPO and ATG antibodies . The absence of TPO usually is associated with no thyroid dysfunction, but the same cannot be said of ATG.

Keywords • Antithyroid antibodies • Antithyroglobulin antibodies • Autoimmune thyroid disease • Hashimoto's thyroiditis • Hyperthyroidism • Hypothyroidism • Thyroid peroxidase antibodies

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Prevalence of Antithyroid Antibodies in Histologically Proven Autoimmune Thyroid Diseases and Correlation with Thyroid Dysfunction in South India

Ajit S. Shinto, MBBS, DRM,DNB,PGDHA, Leena Pachen, BSc, NMT,DNMT,
T.K. Sreekanth, BSc, MRT, DMRIT, Deepu George, MD

Nuclear Medicine Department,
Amala Institute of Medical Sciences,
Amalanagar, Thrissur -555, Kerala, India

Correspondence: Dr. Ajit S Shinto, Nuclear Medicine Dept.,
Amala Institute of Medical Sciences, Amalanagar, Thrissur -555, Kerala, India
Office Tel: 04872304163 Personal cell: 09747714265 Fax: 04872304163
ajitshinto@gmail.com, ajitshinto@yahoo.com

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Keywords Antithyroid antibodies • Antithyroglobulin antibodies • Autoimmune thyroid disease • Hashimoto's thyroiditis • Hyperthyroidism • Hypothyroidism • Thyroid peroxidase antibodies

Introduction

Autoimmunity of the thyroid gland results in a spectrum of thyroid diseases in patients. The patients commonly present in outpatient endocrine clinics with goiter or thyroid dysfunction. Etiologically, patients with autoimmune thyroiditis, including Hashimoto's thyroiditis (chronic autoimmune thyroiditis) which has specific histopathological findings, are usually hypothyroid. Less commonly, patients are hyperthyroid.[1]

Autoimmune thyroiditis shows lymphocytic infiltration with large lymphoid follicles that have germinal centres. In addition, if large thyroid cells have an acidophilic staining character called "Hurthle" or "Askanazy" cells, the diagnosis is Hashimoto's thyroiditis. In this study, all patients with histological findings of autoimmune thyroiditis, with or without histopathological findings of Hashimoto's, are included under the title autoimmune thyroid disease.

The clinical diagnosis of autoimmune thyroid disease is usually confirmed by the detection of various antibodies in the patient's blood sample. Three types of antibodies are most commonly assayed: antithyroglobulin, thyroid peroxidase (previously termed antimicrosomal), and TSH receptor antibodies. TSH receptor antibodies are either stimulating or blocking antibodies; respectfully, these are related to Grave's disease and myxoedema. We do not included in the present study, although their presence is classified as autoimmune thyroid disease. In autoimmune thyroiditis, high circulating blood titres of antithyroglobulin antibodies and antithyroperoxidase antibodies are usually present.

Table I. Classification of autoimmune thyroid disease.

Etiology	Clinical Presentation
Hashimoto's thyroiditis	Goitre, hypothyroidism (rarely hyperthyroidism)
Painless thyroiditis (silent/post partum)	Small goiter, transient hyper- or hypothyroidism
Atrophic/primary thyroiditis	Hypothyroidism/ thyroid atrophy
Grave's disease	Hyperthyroidism /goitre

The clinically pertinent classification of autoimmune thyroid disease, listed in Table 1, includes Hashimoto's thyroiditis and its variants, autoimmune atrophic thyroiditis (myxoedema) and Grave's disease.[2] Prevalence data from the American Thyroid Association state regional variations, but the generally accepted range of women worldwide developing autoimmune thyroiditis at some point in their lives is 5% to 7%. This percentage makes autoimmune thyroid disease a relatively common disorder.[3]

Routine thyroid antibody estimation in patients with thyroid enlargement has revealed an increased prevalence of autoimmune thyroiditis in Kerala.[4] In recent years, the hypothesis has gained ground that entities like puberty goitre in adolescents and multinodular goitre in adults are due to autoimmune thyroiditis. However, these conditions were not previously diagnosed because tests for antibody estimation were not available.[4]

To test this hypothesis, this study has two aims: (1) to find the regional prevalence of thyroid peroxidase and anti-thyroglobulin antibodies, and (2) to determine the relation of the antibody prevalence to thyroid dysfunction in patients with histological diagnoses of autoimmune thyroiditis and Hashimoto's thyroiditis.

Patients and Methods

Included in this study were 100 consecutive patients who attended the outpatient clinic and had a histological diagnosis of autoimmune thyroiditis or Hashimoto's thyroiditis with either symptoms of thyroid dysfunction and/or thyroid swelling. Besides a detailed clinical examination, each patient underwent the following investigations: blood tests for thyroid function (T_3, T_4, TSH), thyroid peroxidase antibodies, and antithyroglobulin antibodies. Each patient also had both a thyroid ultrasound scan and a fine-needle aspiration cytology of the thyroid gland. Thyroid function tests and antibodies were estimated by the chemiluminiscent method.[5]

Each patient's thyroid functional status (euthyroidism, hypothyroidism, or hyperthyroidism) was defined by TSH, free T_4, and free T_3 levels. Following are the values of the reference ranges for thyroid function and antibody tests in our laboratory: T_3 (1.0-to-2.8 nmol/L); T_4 (62-to-148 nmol/L); TSH (0.4-to-5.0 µIU/ml); antimicrosomal antibodies (< 9.0 IU/ml); and antithyroglobulin antibodies (< 60 IU/ml).

Table II. Age distribution of patients.

Age*	Male	Female	Total	%
< 21	1	3	4	4
21-30	4	23	27	27
31-40	2	31	33	33
41-50	2	23	25	25
51-60	0	9	9	9
> 60	0	2	2	2

*Age in years (Age range: 15-to-62 years)

Results

Of 100 patients studied, 91 were females and 9 were males. As stated previously, for analysis of data, both Hashimoto's thyroiditis and autoimmune thyroiditis were classified as autoimmune thyroid disease. Fifty-nine patients (59%) were classified as having Hashimoto's, and 41 patients (41%) were classified as having autoimmune thyroiditis.

The age of the studied patients ranged from 15 to 62 years. Four were less than 21 years of age and most were females. Patients aged less than 45 years made up 68% of the group (Table II). Many of the patients had long standing histories of thyroid dysfunction or goiter before presenting to us. Because of this, the exact ages at onset of thyroid disease was difficult to assess.

Antibody positivity and thyroid function. Thyroid peroxidase antibodies were estimated in all patients; 89 patients (89 %) tested positive and 11 (11%) tested negative. Antithyroglobulin antibody estimation was also done in all patients; 64 patients (64 %) tested positive and 36 patients (36 %) tested negative (Table III).

Table III. Assay results of antibody levels.

Antibody	Positive	Negative	*p* value*
ATG**	64	36	< 0.005
TPO***	89	11	

* *p* value < 0.005 was considered significant.
** Antithyroglobulin Ab. *** Thyroid peroxidase Ab.

Of the 89 patients who were positive for thyroid peroxidase, 54 (60.7 %) were hypothyroid; 6 (6.7 %) were hyperthyroid. and 29 (32.6%) were euthyroid. However, all patients who were negative for thyroid peroxidase antibodies (100%) were euthyroid. This enhances the predictive value of positivity for thyroid peroxidase antibodies and thyroid dysfunction.

Of 64 patients who were positive for antithyroglobulin antibodies, 34 (53.1%) were hypothyroid; 3 (4.7%) were hyperthyroid, and 27 (42.2%) were euthyroid. Also, of the 36 patients who were negative for antithyroglobulin antibodies, 21 (58.3%) were hypothyroid, and 3 (0.08%) were hyperthyroidism. At the time of the first visit to our clinic, 55% of patients were hypothyroid, 6% were hyperthyroid, 39% were euthyroid. In predicting hypothyroidism (Table IV), thyroid peroxidase antibodies were much more sensitive than antithyroglobulin antibodies (98.1% vs 61.8%).

Ultrasound findings. Ultrasound testing show that 54 patients had multinodular goiter, 16 had diffuse goiter, 2 had cystic thyroid nodules, 3 had solitary nodules, and 25 had features of thyroiditis (i.e., diffuse or focal coarse echo texture in the thyroid gland and increased vascularity—generalized or focal thyroiditis). Of the 3 patients whose autoimmune thyroid disease included solitary nodules, 2 had histological evidence of papillary carcinoma (Table V).

Discussion

Historically, the first thyroid autoantibody discovered was antithyroglobulin antibody. That was in 1956. Antibodies to other antigens present in the cytoplasm of thyroid follicular cells (first termed "antimicrosomal antibodies") were detected in 1976. These "cytoplasmic" antigens were later found to be the enzyme thyroid peroxidase; hence today, these antibodies are more often called "thyroid peroxidase antibodies." Thyroid peroxidase antibodies appeared to be much more prevalent than antithyroglobulin antibodies.[6,7]

Table IV. Correlation between antibody levels and thyroid status.

Antibody assay	Status	Number of patients	Number and % of hypothyroid patients	Number and % of hyperthyroid patients	Number and % of euthyroid patients
ATG*	Positive	64	34 (53.1%)	3 (4.7%)	27(42.2%)
	Negative	36	21 (58.3%)	3 (8.3 %)	12 (33.3%)
TPO**	Positive	89	54 (60.7%)	6 (6.7%)	29 (32.6%)
	Negative	11	1 (9.09%)	0	10 (90.9%)

* Antithyroglobulin Ab. ** Thyroid peroxidase Ab.

The prevalence of autoimmune thyroiditis is increasing. We observed that about 70% of patients who present to outpatient clinics in our geographical region with thyroid problems have autoimmune thyroiditis. The prevalence of positive thyroid antibodies was 29% in pregnant patients in a region similar to ours.[8]

Hypothyroidism is the characteristic functional abnormality in autoimmune thyroid diseases. However, inflammation of the thyroid gland early in the disease may cause thyroid follicular destruction with thyroid hormonal release from the follicles. This results in transient hyperthyroidism.

These antibodies can even lyse the thyroid cells. B cells present the thyroid antigen to T cells. T cells secrete cytokines that activate a variety of other immune cells, and has a role in antibody production (Th2 cells) and apoptotic destruction of thyroid cells by activating cytotoxic T cells (Th1 cells).

Genetic and environmental factors such as toxins, bacterial and viral infections or iodine excess, appear to interact, leading to the appearance of auto antigens and accumulation of antigen-presenting cells in the thyroid. Consequently, due to loss of immune tolerance, auto-reactive immune cells (T lymphocytes) activated by antigen-presenting cells invade the thyroid gland, interacting with the thyroid cells, and the apoptotic pathways are activated by certain cytokines produced locally by the T lymphocytes. It is likely that the regulation of apoptosis during this interaction between the invading lymphocytes and the defending thyroid cells, may play an important role in the clinical expression of autoimmune thyroid diseases.

Table V. Ultrasound scan findings.

Multinodular goitre	54
Cystic nodules	2
Thyroiditis features	25
Solitary thyroid nodule	3
Diffuse Goitre	16
Total	100

Of the patients in this study, 91% were female, and 84% of these were in the reproductive age group. Since thyroid dysfunction can lead to antenatal and neonatal complications, the diagnosis and correction of any thyroid disorder is very important in pregnant patients. Thyroid autoimmunity is a risk factor for pregnancy loss.[9] Some authors have reported that pregnant euthyroid females who are positive for thyroid peroxidase (antimicrosomal) antibodies and who undergo thyroid hormone therapy may improve their miscarriage rate by 75% and their premature deliveries rate by 69%.[10] A higher prevalence of thyroid antibodies also increases the risk of postpartum thyroiditis.[11]

Ultrasound scans revealed that a majority of our patients (54%) had thyroid gland multinodularity, and 16% were had diffuse goiters. Another 2% had papillary thyroid carcinoma.

In the latter 2% of patients, fine-needle aspiration cytology of thyroid gland from multiple sites was a must in view of the association of papillary carcinoma with autoimmune thyroid diseases. Here a pertechnetate thyroid scan can be used to assess functionality of the thyroid nodules before fine-needle aspiration cytology is considered. This procedure may identify the dominant and cold nodules which should not be missed.

Sixteen percent of the patients had no thyroid swelling but showed evidence of thyroiditis during ultrasound thyroid scans. In six patients with histologically proven autoimmune thyroiditis, no autoantibodies were detected in the blood; this suggests that autoimmune thyroiditis cannot be completely excluded in patients with no antibodies.

Positive antibodies were detected in the neonates of 4 patients who were positive for both thyroperoxidase and antithyrogobulin antibodies. Hence it appears prudent to test the offspring of women who are positive for both type of antithyroid antibodies, to diagnose any thyroid affliction in the neonates early. Since we have not done neonatal antibody screening routinely in all the patients postpartum, no conclusion could be drawn from this finding.

SUMMARY

Autoimmune thyroiditis is definitely not a rare disease, but it is under diagnosed. Each patients who has a swollen thyroid gland should be subjected to thyroid function tests and antibody estimation followed by fine-needle aspiration cytology. If all these tests favor of a diagnosis of autoimmune thyroiditis, surgery is not urgent unless the patient has symptoms of pressure, rapid thyroid gland enlargement, or suspicion of malignancy.

Hypothyroidism was the most frequent thyroid dysfunction in patients who were positive for thyroid peroxidase (60%) and antithyroglobulin antibodies (53.1%). It should be noted that only one subject who was negative for thyroid peroxidase was hypothyroid. However, 58.3% of patients who were negative for antithyroglobulin antibodies were hypothyroid. This shows that thyroid peroxidase antibodies are more sensitive than antithyroglobulin antibodies in predicting hypothyroidism.

Similarly, thyroid peroxidase antibodies were more sensitive than antithyroglobulin antibodies in autoimmune thyroiditis (98.1% vs 61.8%, $p < 0.005$). It is well recognized that autoimmune thyroid disease correlates with excess iodine intake; hence, the increased prevalence of thyroiditis may be related to the intake of iodine-rich salt by the majority of the sea-fish consuming population of Kerala (a southern coastal state in India where the study was conducted). However, the definite correlation of excess iodine intake and thyroiditis warrants study of the plasma and urinary iodide levels and thyroid iodine uptake levels in this population.

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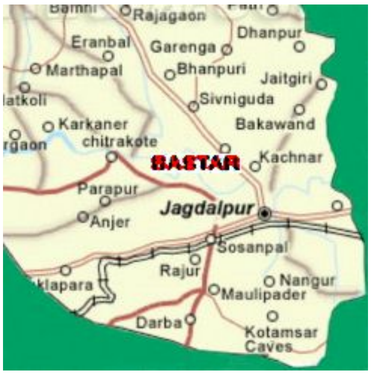

Thyroid Science 6(6):1-5, 2011

Thyroid Dysfunctions in Tribal Women of the Bastar Region of Chattisgharh, India

Full Text Free (pdf)

Lincy K. Skaria, MSc,[1*] Purnima Dey Sarkar, MSc, PhD,[2]
Gopinath Agnihotram, MSc,[1] Amar Singh Thakur, MSc, PhD,[1]
Girish Pamidamarri, Msc[1]

[1]Govt. Medical College, Jagdalpur, (C.G.) 494001, India
[2]MGM Medical College, Indore, MP, India

**Correspondence*: Mrs. Lincy K. Skaria, Assistant professor
Department of Biochemistry, Govt. Medical College
Jagdalpur, Chattisgharh-494001, India.
Email: linsey@rediffmail.com, Phone: 09754158156

***Abstract*. Introduction**: The Bastar region receives heavy rainfall and frequent flooding, leading to depletion of iodine from the superficial soil layer. Also, consumption of sea food is deficient in this area. Hence, these sources of iodine deficiency raises concerns about the thyroid status of Bastar residents. Thyroid dysfunction is a common endocrine disorder that has signs and symptoms that mimic those of other common diseases. **Methods**: The signs and symptoms of 150 subjects who visited the General Medicine Department, Govt. Medical College, in Jagdalpur raised the possibility that they had thyroid disease. That their signs and symptoms were not explained by non-thyroid diseases constituted the study inclusion criterion. The subjects were analyzed for levels of tri-iodothyronine (T3), tetra-iodothyronine (T4), and thyroid stimulating hormone (TSH). Data was analyzed by Anova tests and correlation analyses. **Results**: Based on their thyroid hormone and TSH levels, subjects were classified into four groups: 20.66% were euthyroid, 59.33% were hypothyroidism, 12.66% had subclinical hypothyroidism, and 7.33% were hyperthyroidism. Some males (n = 15, 10%) but mostly females (n = 135, 90%) were included in the study. T3, T4 and TSH levels significantly differed between all four groups ($p < 0.001$). The study also analyzed the correlation between T3, T4 and TSH in different groups. **Conclusion**: Subclinical hypothyroidism should be treated with thyroid hormone therapy to prevent progression to overt hypothyroidism and other clinical manifestations. Inclusion of non-goitrogenic foods and exclusion of goitrogenic foods also should be recommended to patients who have thyroid dysfunction.

Keywords • Hypothyroidism • Hyperthyroidism • Subclinical hypothyroidism • Thyroid stimulating hormone • Tri-iodothyronine (T3) • Tetra-iodothyronine (T4)

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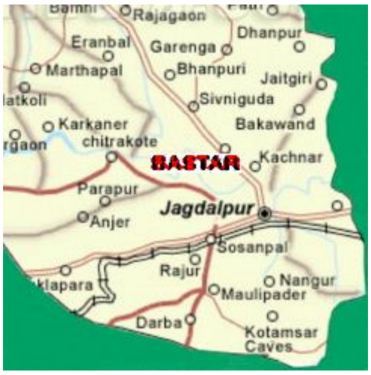

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Thyroid Science 4(11):CLS1-3, 2009

Study of Various Treatment Modalities in 107 Cases of Solitary Thyroid Nodule in Central India

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Dr Anil Sunkara, MBBS[1] Dr Kiran Kher, MS (General Surgery)[2]

[1]Resident. [2]Professor
Department of Surgery, Jawaharlal Nehru Medical College
Sawangi (Meghe), Wardha 442004, Maharashtra, India

**Correspondence*: Dr. Anil Sunkara
docanil@hotmail.com Mobile: 091-9960413456

ABSTRACT: **Introduction**. The Solitary thyroid nodule is defined as a palpably discrete swelling within an otherwise apparently normal gland and is usually a benign lesion. Screening of large numbers of patients previously unsuspected of having goitre suggests that the incidence of isolated thyroid nodule in the general population may be of the order of 1% to 5%. Despite of the high frequency of thyroid nodule in the general population, the occurrence of thyroid carcinoma in solitary thyroid nodule is rare (5-20% OR 40/1 million). It is thus a challenge to select from this large group of patients with thyroid nodules, those who require further investigation and perhaps surgical therapy. **Aims & Objectives**. To evaluate the various treatment modalities in solitary thyroid nodules with minimal morbidity. **Materials and methods**. The patients were subjected to aspiration, hemi thyroidectomy, subtotal or total thyroidectomy depending upon the clinical sonographic and cytologic diagnosis and the surgeons preference. **Observations**. Thus various therapeutic procedures were performed on all 107 cases. The cystic nodules which disappeared on aspiration were discharged and followed up on regular intervals. The rest of the cases underwent hemi thyroidectomy, total and subtotal based on the size, gland involvement and cytology. **Conclusion**. Preoperative evaluation with ultrasound and fine needle aspiration cytology can minimize the extent of surgery to be performed. Most of the times the solitary thyroid nodule harbors a benign pathology.

Keywords. • Fine-needle aspiration cytology • Thyroidectomy • Thyroid nodule

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Thyroid Science 6(1):1-3, 2011

Outcome of Fixed and Uncalculated Dose of Radioiodine in the Treatment of Hyper Functioning Thyroid Nodules

Full Text Free (pdf)

Morteza Taghavi, MD[1] and Hatami Ghazal, MD[2]

[1]Assistant Professor of Endocrinology, Endocrine Research Center
Mashhad Medical University, Ahmad Abad Street, Ghaem Hospital, Mashhad, Iran

[2]Hatami Ghazal, MD
Ahmad Abad Street, Ghaem Hospital, Mashhad, Iran

Corresponding author: Morteza Taghavi, MD
Assistant Professor of Endocrinology, Endocrine Research Center
Mashhad Medical University, Ahmad Abad Street, Ghaem Hospital, Mashhad, Iran
Phone: 00989155164037 Fax: 00985118406757
mortezataghavi2003@yahoo.com and taghaviMR@mums.ac.ir

***Abstract*. Introduction**: This is a prospective study of patients treated for a solitary toxic nodule with a fixed dose of radioiodine (131I) and followed for at least 1 year in Mashhad, north east of Iran. **Methods**: We evaluated 780 patients who presented to the university hospital of Ghaem during a 7-year period because they had at least one thyroid nodule. We found hot thyroid nodules in 95 (12%) patients. Of these patients, 86 (90.5%) were female and 9 (9.5%) were male. Sixty-nine (72.6%) of the patients had thyrotoxicosis and 26 (27.4%) were euthyroid. We treated 49 thyrotoxic patients with 131I and followed them for a minimum of 12 months. The 131I dose for all patients was 15 mCi. The patients underwent thyroid function testing before treatment, at 6 months after treatment, and, thereafter, once every year. **Results**: The single fix dose (15 mCi) of radioiodine was sufficient to control hyperthyroidism in most patients (46/49, 93.8%) in 6 months. Because of persistent hyperthyroidism 6 months after the first dose, 3 patients (6.2%) required a second dose. **Conclusion**: A cure rate of 93.8% can occur within 6 months with a fixed and uncalculated dose of radioiodine. This result is similar to the results of treatment with calculated dose of radioiodine.

Keywords • Hot thyroid nodule • Radioiodine • Thyrotoxicosis

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Outcome of Fixed and Uncalculated Dose of Radioiodine in the Treatment of Hyper Functioning Thyroid Nodules

Morteza Taghavi, MD[1] and Hatami Ghazal, MD[2]

[1]Assistant Professor of Endocrinology, Endocrine Research Center
Mashhad Medical University, Ahmad Abad Street, Ghaem Hospital, Mashhad, Iran

[2]Hatami Ghazal, MD
Ahmad Abad Street, Ghaem Hospital, Mashhad, Iran

Corresponding author: Morteza Taghavi, MD
Assistant Professor of Endocrinology, Endocrine Research Center
Mashhad Medical University, Ahmad Abad Street, Ghaem Hospital, Mashhad, Iran
Phone: 00989155164037 Fax: 00985118406757
mortezataghavi2003@yahoo.com and taghaviMR@mums.ac.ir

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Keywords Hot thyroid nodule • Radioiodine • Thyrotoxicosis

Introduction

Thyroid tissue nodularity is common. In the large Framingham, MA study, clinically apparent thyroid nodules were present in 6.4% of women and 1.5% of men.[1] The use of ultrasonography showed that 20% to 76% of women had at least one thyroid nodule.[2,3]

Fifteen percent of thyroid nodules are hot. Hot nodules are caused by hyperplasia of thyroid follicular cells whose functional capacity is independent of regulation by TSH. Activation of somatic mutations of the TSH-receptor gene or Gs-alpha protein[4,5] have been found in toxic adenoma; but mutations of the TSH-receptor gene are the most common cause.[6-10]

Radioiodine (^{131}I) is widely and successfully used for therapy of patients with toxic adenomas.[11] The aim of this study was two-fold: (1) to evaluate the incidence of and acquire demographic data on patients with hot thyroid nodules in Mashhad, north east of Iran; (2) to determine the outcome for patients treated with a fixed dose of radioiodine therapy.

Materials and Methods

During 7 years (May 2002 to April 2009), 780 patients with thyroid nodules presented to the university hospital of Ghaem and were evaluated. Hot thyroid nodules were found in 95 (12%) of the patients.

The diagnosis of a hot nodule was based two factors: (1) the patient had a palpable thyroid nodule corresponding to an area of increased radioiodine concentration on 99mTc-pertechnetate scintigraphy, and (2) suppressed radioiodine uptake in surrounding and contralateral parts of the gland. The diagnosis of hyperthyroidism was based on the clinical picture and thyroid function testing. Overt hyperthyroidism is defined as a suppressed TSH with high thyroid hormones levels; subclinical hyperthyroidism is defined as a suppressed TSH with normal thyroid hormone levels.

The 49 thyrotoxic patients treated with ^{131}I were followed for a minimum of 12 months. The ^{131}I dose for all patients was 15 mCi. Thyroid function tests were performed before ^{131}I treatment, 6 months after treatment, and, thereafter, once every year.

Statistical Evaluation: Quantitative data were presented as mean ± SD. For statistical evaluation, the Mann-Whitney test and chi-square were used. The level of significance was chosen as $P < 0.05$.

Results

Studies were conducted of 780 patients who had thyroid nodules. Of the 95 patients (12.2%) who had hot thyroid nodules, the mean age was 44.8 ± 15.35. Of these 95 patients, 86 (90.5%) were female and 9 (9.5%) were male. Sixty-nine (72.6%) of patients had thyrotoxicosis (clinical or subclinical) and 26 (27.4%) were euthyroid (Table 1).

Table 1. Characteristic of patients.

Age (years)		44.8 ± 15.35
Sex	Males	86 (90.5%)
	Females	9 (9.5%)
Thyroid status	Hyperthyroid	69 (72.6%)
	Euthyroid	26 (27.4%)
Nodule size (cm)	< 4	44
	≥ 4	51

The mean size of hot nodules was 4.1 centimeters in its largest diameter. Hyperthyroidism at the time of diagnosis was positively correlated with the size of the nodule ($P < 0.01$).

Radioiodine was given as a single uncalculated dose in 49 patients This single fixed dose (15 mCi) of radioiodine was sufficient to control hyperthyroidism in most of patients (46/49, 93.8%) in 6 months. Due to persistent hyperthyroidism 6 months after the first dose, 3 patients (6.2%) required a second dose. Nobody became hypothyroid during follow-up periods.

No significant differences were seen in the initial thyroid nodule size or thyroid function test results between patients who needed only one ^{131}I treatment and those who need more than one ^{131}I treatment.

Discussion

Toxic adenoma is a common cause of hyperthyroidism. The classic presentation for toxic adenoma is a palpable thyroid nodule. The nodule corresponds to an area of increased radioiodine concentration on thyroid scintigraphy in a hyperthyroid patient.

There are three main ways to treat a toxic adenoma: medical therapy with a thioamides that should continue indefinitely, radioiodine, or surgery.

Radioiodine is widely used for therapy of patients with toxic adenomas and is recognized as a safe and effective treatment.[11] It rapidly concentrates in a toxic nodule and causes destruction of the adenoma. Most patients remain euthyroid after radioiodine therapy because the radioiodine mostly accumulates in the hyperfunctioning nodules.[12] for complete treatment of thyrotoxicosis, 10% to 20% of patients may need a second or subsequent dose of radioiodine.

In a large study of 364 patients with hot nodules treated with calculated dose of radioiodine due to nodule size and RAIU, similar results were obtained. A single ^{131}I administration was sufficient to control overt or subclinical hyperthyroidism in 94% of patients.[13]

Other studies have included 53, 45, 52, 27, and 62 patients with hot thyroid nodules. Calculated doses of radioiodine was effective in 75% (14), 93 % (15), 98% (16), 93% (17), and 86% (18) of cases.

In the present study, we analyzed the outcome of 49 patients with hyperfunctioning thyroid nodules treated with 15 mCi ^{131}I at our university hospital during 7 years. We show the effectiveness of an uncalculated fixed dose of radioiodine to treat subclinical or overt hyperthyroidism in 93.8% of our patients. Only 3 patients (6.2%) required a second dose for complete cure of their thyrotoxicosis. Thyroid status and the nodule size did not correlate with the outcome of ^{131}I therapy, as observed by others.[19,20]

Conclusion

Radioiodine is an effective treatment of thyroid hot nodules even with a fixed and uncalculated dose. A cure rate of 93.8% can occur within 6 months. This result is similar to the results of treatment with calculated doses of radioiodine.

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Autoimmune Thyroiditis in Patients with Myelopathy/Tropical Spastic Paraparesis and in HTLV-1 Carriers in Mashhad, Northeastern Iran

(Full Text Free in pdf format)

Morteza Taghavi, MD,* Seddigheh Fatemi, MD,**
Hosein Ayatollahi,† Houshang Rafatpanah, PhD‡

*Assistant Professor of Endocrinology, Endocrine Research Center, Mashhad
Medical University, mortezataghavi2003@yahoo.com and taghaviMR@mums.ac.ir
**Immunology Department, Bu Ali Research Center, Mashhad Medical University, fatemis1@mums.ac.ir
†Assistant Professor of Pathology, Mashhad Medical University, hosseinayatollahih@mums.ac.ir
‡Immunology Department, Mashhad Medical University, Horary Research Assistant of the
University of Manchester, rafatpanahh@mums.ac.ir

Contact: Dr. M. Taghavi mortezataghavi2003@yahoo.com

ABSTRACT. There are some reports about the association of autoimmune thyroid diseases with human T-cell leukemia virus type-I (HTLV-I) infection. The objective of this study was to estimate the seroprevalence rates of antithyroid antibodies in HTLV-I carriers and HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients in Mashhad, northeastern Iran, in order to determine any association between HTLV-I infection and Hashimoto's thyroiditis (HT).

Methods: Forty-six HTLV-I infected patients (24 patients with HAM/TSP and 22 asymptomatic carriers) and 40 HTLV-I seronegative healthy individuals were screened for the presence of thyroid autoantibodies. The diagnosis of Hashimoto's thyroiditis was based on the presence of positive thyroid autoantibodies (antithyroid peroxidase and/or antithyroglobulin) and at least one of two additional criteria (hypothyroidism and/or goiter). Analysis of the data was done using the Fisher-Exact test and SPSS statistical software version 13.0. Any P value below 0.05 was considered statistically significant.

Results: We found thyroid autoantibodies in 14 (63.6%) of 22 asymptomatic carriers, 6 (25%) of 24 patients with HAM/TSP, and 3 (7.5%) of 40 HTLV-I seronegative healthy individuals. We found Hashimoto's thyroiditis in 45.4% of asymptomatic carriers, 25% of HAM/TSP patients, and 5% of seronegative healthy individuals. The percentage of patients with Hashimoto's thyroiditis was significantly higher ($P<0.01$) than the percentage in healthy seronegative individuals.

Conclusion: This study demonstrates a high prevalence of Hashimoto's thyroiditis in the HAM/TSP patients and the HTLV-I carriers in Mashhad. Our findings suggest an association between HTLV-I infection and Hashimoto's thyroiditis in our region.

Keywords. Hashimoto's thyroiditis • HTLV-1 • Mashhad, Iran • Myelopathy/tropical spastic paraparesis • Thyroglobulin antibodies • Thyroid peroxidase antibodies

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Morteza Taghavi, MD,* Seddigheh Fatemi, MD,**
Hosein Ayatollahi,† Houshang Rafatpanah, PhD‡

*Assistant Professor of Endocrinology, Endocrine Research Center, Mashhad Medical University, mortezataghavi2003@yahoo.com and taghaviMR@mums.ac.ir
** Immunology Department, Bu Ali Research Center, Mashhad Medical University, fatemis1@mums.ac.ir
† Assistant Professor of Pathology, Mashhad Medical University, hosseinayatollahih@mums.ac.ir
‡ Immunology Department, Mashhad Medical University, Horary Research Assistant of the University of Manchester, rafatpanahh@mums.ac.ir

Contact: Dr. M. Taghavi mortezataghavi2003@yahoo.com

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Introduction

Human T-cell leukemia virus type-I (HTLV-I) is a human retrovirus endemic in southern Japan, intertropical Africa, Melanesia, Latin America, and the Caribbean basin.[1] HTLV-I is etiologically associated with adult T-cell leukemia[2] and HTLV-I-associated myelopathy/tropical spastic paraparesis (HAM/TSP).[3][4] HTLV-I may also cause some other inflammatory disorders such as uveitis,[5] chronic arthropathy,[6] pulmonary alveolitis,[7] and Sjögren's syndrome.[8] The possible role of HTLV-I in thyroid diseases was initially raised by reports of Hashimoto's thyroiditis in HTLV-I carriers and patients with HAM/TSP.[9][10] Graves' disease has also been observed in HTLV-I carriers.[11][12] HTLV-I seropositivity has been a risk factor for thyroid disorders in epidemiological studies in Japan.[10][13][14][15]

The possible pathogenic role of HTLV-I in thyroid diseases is supported by many findings: HTLV-I envelope protein and tax mRNA have been detected in follicular epithelial cells of the thyroid tissues of a patient with Hashimoto's thyroiditis;[16] tax mRNA was also found in infiltrating lymphocytes in the interfollicular space;[16] and HTLV-I proviral DNA and HTLV-I have been detected in the thyroid tissue of patients with Hashimoto's thyroiditis and Graves' disease.[16][17]

The virus is also endemic in Mashhad in northeastern Iran.[18] To our best knowledge, there has been no study in our region of the prevalence of Hashimoto's thyroiditis among HTLV-I carriers or among HAM/TSP patients. This study had two objectives: to estimate the seroprevalence rates of antithyroid antibodies in HTLV-I carriers and HAM/TSP patients in Mashhad, and to determine whether we would find an association in the patients between Hashimoto's thyroiditis and HTLV-I.

Methods and Patients

Blood samples were collected from 46 HTLV-I infected patients, 22 asymptomatic carriers (13 females and 9 males, 22-70 years old, mean age: 42.58±14.49), and 24 patients with HAM/TSP (17 females and 7 males, 17-64 years old, mean age: 38.04±11.04). Forty HTLV-I seronegative healthy individuals (26 female and 14 males, 17-65 years old, mean age: 36.84±16.32) served as normal controls. The control subjects did not have a history of thyroid or autoimmune diseases.

The diagnosis of Hashimoto's thyroiditis was based on the presence of positive thyroid autoantibodies, thyroid peroxidase (TPO) and/or thyroglobulin (Tg), and at least one of two additional criteria: hypothyroidism and/or goiter. Antibodies to TPO and Tg were determined by RIA (Aeskalisa a-TPO, Orgentec Diagnostica, Germany). Diagnosis of HAM/TSP was based on the World Health Organization diagnosis guidelines.[19] All patients (HTLV-I asymptomatic carriers and those with HAM/TSP) and all HTLV-I-seronegative healthy controls were Iranians living in Mashhad (HTLV-I endemic city), the northeast area of Iran.

Statistical Analyses

Data were descriptively expressed as mean±SD or number and percent. Statistical analysis was done by using the Fisher-Exact test with statistical software SPSS version 13.0. Any P value below 0.05 was considered statistically significant. The Endocrine Research Committee of Mashhad University reviewed all aspects of the research and approved the protocol.

Results

Thyroid autoantibodies were positive in 14 (63.6%) of 22 asymptomatic carriers, 6 (25%) of 24 patients with HAM/TSP, and 3 (7.5%) of 40 HTLV-I seronegative healthy individuals. In the HTLV-I carrier groups, 4 patients had subclinical hypothyroidism and 6 patients had euthyroid firm goiter. In the HAM/TSP group, 4 patients had subclinical hypothyroidism and 2 patients had euthyroid firm goiter. Seronegative healthy individuals were euthyroid and 2 of them had firm goiter. Hashimoto's thyroiditis was found in 45.4% of asymptomatic carriers, 25% of HAM/TSP patients, and 5% of seronegative healthy individuals. Therefore, the percentage of patients with Hashimoto's thyroiditis was significantly higher ($P<0.01$) than the percentage in healthy seronegative individuals.

Discussion

HTLV-I is a human retrovirus endemic in some areas of the world.[1] HAM/TSP is the major syndrome caused by HTLV-I, but the virus may also cause a systemic immune-mediated inflammatory disease involving many tissues including the thyroid gland. Correlation of autoimmune thyroid diseases and HTLV-I infection were investigated recently, and the role of HTLV-I in the pathogenesis of autoimmune thyroid diseases has been demonstrated in animals and humans.[20][21][22][23][24]

Genetic factors including human leukocyte antigen and cytotoxic T lymphocyte antigen-4 (CTLA-4) are involved in autoimmune thyroid diseases.[25][26] However, HTLV-I infection is not associated with CTLA-4 polymorphisms in either Hashimoto's thyroiditis patients or controls.[27] HTLV-I infection, then, does not appear to be regulated by genetic factors, and it may cause Hashimoto's thyroiditis as an independent, purely environmental factor.

The HTLV-I proviral load is thought to be a major determinant of HTLV-I-associated diseases. The proviral load is higher in the peripheral blood of patients with HAM/TSP than in the blood of asymptomatic carriers.[28] It is also higher in the peripheral blood of HTLV-I-infected patients with either Hashimoto's thyroiditis or Graves' disease than in

HTLV-I asymptomatic carriers.[29] Similarly, patients with HTLV-I-associated uveitis and HTLV-I-seropositive patients with arthritis or connective tissue disease have a higher proviral load than asymptomatic carriers.[30][31]

Involvement of HTLV-I in the pathogenesis of autoimmune thyroid disease in Japan, where this retrovirus is endemic, has been extensively investigated. Kawai et al. reported that the prevalence of HTLV-I antibodies in Hashimoto's thyroiditis patients, residents of the Tokushima and Kochi prefectures in Japan, was 6.3%, which was significantly higher than the expected frequency of 2.2%.[10]

Mizokami et al. also reported that the prevalence of HTLV-I antibodies was significantly higher in patients with either antithyroid antibody-positive chronic thyroiditis (7.4%) or Graves' disease (7%) than the expected frequency in Fukuoka prefecture, Japan.[13] Mine et al. found that the frequency of antithyroid antibodies in blood donors with HTLV-I antibodies was significantly higher (7.9%) than that in control donors without the HTLV-I antibodies.[14] Akamine et al. also found a high prevalence of positivity for thyroid autoantibodies in adult T-cell leukemia patients (40.4%) and HTLV-I carriers (30%).[15]

Mashhad, a city in northeastern Iran, is also an endemic area for HTLV-I.[18] The present study determined the seroprevalence rates of antithyroid antibodies in HTLV-I carriers and HAM/TSP patients for the first time in Iran. The study also provides data supporting the role of HTLV-I in the development of thyroid diseases in our region.

Hashimoto's thyroiditis was found in 45.4% of asymptomatic carriers of HTLV-I and 25% of HAM/TSP patients. These percentages were significantly higher ($P<0.01$) than the percentage of Hashimoto's thyroiditis in healthy seronegative individuals (5%).

Conclusion

This study demonstrates a high prevalence of positivity for antithyroid autoantibodies and Hashimoto's thyroiditis in HAM/TSP patients and HTLV-I carriers in Mashhad. There is, then, an association between HTLV-I infection and Hashimoto's thyroiditis in our region.

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"Positive HTLV-I in Graves' patients in North East Iran.">

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Incidence of Seropositivity for HTLV-I in Patients with Graves' Disease in Mashhad, North East of Iran

Full Text Free in pdf format

Morteza Taghavi,* Afkhami Z. Mojgan, Abutorabi Robab,
Bonakdaran Shokufeh, and Rajabian Reza

Endocrinology Research Center, Mashhad Medical University,
Ahmad Abad Street, Ghaen Hospital, Mashhad, Iran

**Corresponding author:* Dr. Morteza Taghavi, Assistant Professor of Endocrinology,
Endocrine Research Center, Mashhad Medical University, Ahmad Abad Street,
Ghaen Hospital, Mashhad, Iran. Phone: 00989155164037 Fax: 00985118406757,
mortezataghavi2003@yahoo.com, taghaviMR@mums.ac.ir

ABSTRACT. Graves' disease is an autoimmune thyroid disease and is the most common cause of thyrotoxicosis. Viral infections are frequently cited as a major environmental factor contributing to autoimmune thyroid diseases. Some reports indicate that the incidence of human T-cell leukemia virus type I (HTLV-I) antibody is higher in patients with Graves' disease. The objective of this study was to determine whether HTLV-I infection and Graves' disease are related. Our method was to determine the seropositivity rate of HTLV-I in patients with Graves' disease in Mashhad, an endemic city in north east Iran. We recruited all patients with Graves' disease who consecutively attended our endocrinology clinic at the University Hospital of Mashhad. Blood samples were collected from 105 Graves' patients. We screened the patients' serum for HTLV-I using an enzyme-linked immunosorbent assay. We then compared the seroprevalence of HTLV-I in the patient group with the viral infection rate calculated for the entire population of blood donors in Mashhad. No cases in our patient group were positive for HTLV-1 (0/105 = 0%). By comparison, the control group had a seropositivity of 0.664% (404/60,892). In this study, we found no association between HTLV-I and Graves' disease in Mashhad. Further studies are needed to determine whether there is a relationship between the two conditions.

Keywords. Graves' disease • HTLV-I • Human T-cell leukemia virus type I • Iran • Mashhad

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Morteza Taghavi,* Afkhami Z. Mojgan, Abutorabi Robab,
Bonakdaran Shokufeh, and Rajabian Reza

Endocrinology Research Center, Mashhad Medical University,
Ahmad Abad Street, Ghaen Hospital, Mashhad, Iran

**Corresponding Author:* Corresponding author: Dr. Morteza Taghavi, Assistant Professor of Endocrinology,
Endocrine Research Center, Mashhad Medical University, Ahmad Abad Street, Ghaen Hospital, Mashhad, Iran.
Phone: 00989155164037 Fax: 00985118406757, mortezataghavi2003@yahoo.com, taghaviMR@mums.ac.ir

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Introduction

Human T-cell leukemia virus type I (HTLV-I) is a human retrovirus endemic to southern Japan, intertropical Africa, Melanesia, Latin America, and the Caribbean basin.[1] The virus is a causative agent in adult T-cell leukemia[2] and HTLV-I-associated myelopathy/tropical spastic paraparesis.[3,4] HTLV-I may also be the cause of some other inflammatory disorders, such as uveitis,[5] chronic arthropathy,[6] pulmonary alveolitis,[7] Sjögren's syndrome,[8] and autoimmune thyroiditis.[9-13]

The autoimmune thyroid diseases, which are common, include Hashimoto's thyroiditis and Graves' disease. Both disease are characterized by lymphocytic infiltration and the presence of serum antithyroid antibodies. The association of autoimmune thyroiditis and HTLV-I has been extensively investigated, and there are reports of a correlation between Graves' disease and uveitis in HTLV-I carriers (14,15). The virus is endemic in Mashhad in northeastern Iran.[16] We recently reported an association between Hashimoto's thyroiditis and HTLV-I in Mashhad.[17] The objective of this study was to determine whether there is an association in Mashhad between Graves' disease, another common autoimmune thyroid disease, with HTLV-I.

Materials and Methods

We recruited all patients with Graves' disease who consecutively attended our endocrinology clinic in the University Hospital of Mashhad between February 1, 2008 and March 30, 2009. After the aim of the study was explained to the patients, those who gave informed consent were asked to participate.

Blood samples were collected from 105 patients with Graves' disease. Serum samples were screened for HTLV-I using an enzyme-linked immunosorbent assay (ELISA; Dia. Pro diagnostic Bioprobes, Italy).

Data were descriptively expressed as mean ± SD or number.

To compare the seroprevalence rate of HTLV-I found in Graves' disease with that of the society at large, we used the viral infection rate calculated for the entire population of blood donors in Mashhad (n = 60,892) referred to the Blood Transfusion Organization between March 2001 and March 2002.[16]

Results

A total of 105 patients with Graves' disease were tested for HTLV-I. The patients included 36 males and 69 females who ranged in age from 17-68 years. The mean age of the group was 34.31 ± 11.52 years. All patients were Iranian and living in Mashhad (an HTLV-I endemic area), north east of Iran.

No Graves' patients were positive for HTLV-1. Therefore, the seropositivity rate for the patient group was 0% (0/105) compared to 0.664% (404/-60,892) for the control group.

Discussion

Graves' disease is a common autoimmune disease and is considered the most common cause of thyrotoxicosis. Specific infections may trigger Graves' disease. They may do so by initiating the liberation of antigens (via cell destruction or apoptosis), by forming altered antigens or causing molecular mimicry, by cytokine and chemokine secretion, and by inducing aberrant HLA-DR expression and Toll-like receptor activation.[18] Viral infections are often cited as a major environmental factor that initiates autoimmune thyroid diseases.[9-13]

HTLV-I is a human retrovirus endemic to some areas of the world.[1] The virus may cause a systemic immune-mediated inflammatory disease that involves many tissues, including the thyroid gland. The role of HTLV-I in the pathogenesis of autoimmune thyroid diseases has been demonstrated in animals and human.[19-23] Most of these studies have involved patients with Hashimoto's thyroiditis. However, researchers have reported that in Fukuoka Perfecture, Japan, the incidence of HTLV-I antibody in Graves' patients is higher (6.6%) than expected in the general population (2.2%).[11]

Anti-HLTV-I antibodies and proviral DNA has been detected in the peripheral lymphocytes of Graves' patients.[24,25] In addition, proviral load in HTLV-I-infected patients with Graves' disease was significantly higher than in asymptomatic HTLV-I carriers.[26] It appears that Graves' disease and HTLV-I infection interact and result in the onset of uveitis.[24,25] The provirus load was significantly higher in uveitis patients with Graves' disease than in those without Graves' disease.[28] As in Hashimoto's thyroididtis, HTLV-I infectivity in the thyroid was proven: HTLV-I DNA was detected by polymerase chain reaction in the thyroid tissue of an HTLV-I-infected male who was afflicted with Graves' disease followed by uveitis. Also, HTLV-I was isolated from thyroid tissue by coculture with peripheral blood lymphocytes.[29]

There is some evidence of HTLV-I or its components in the organs of patients with Graves' disease. However, it remains to be determined whether the virus is responsible for the thyroid disease or whether it is just innocent bystanders. There are only limited epidemiologic studies of the role of HTLV-I in Graves' disease.[11]

In this study we evaluated the incidence of serum positivity for HTLV-I among Graves' patients in Mashhad, an endemic city in Iran. Contrary to the results reported by Mizokami et al.,[10] we found no association between HTLV-I and Graves' disease. None of our patients with Graves' disease were infected with HTLV-I.

Conclusion

We found no correlation between HTLV-I and Graves' disease. Further studies are needed to clarify the relationship between viruses and autoimmune thyroid diseases, including HTLV-I and Graves' disease.

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Intensity Modulated Radiation Therapy (IMRT) for Thyroid Cancer

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[1]Aruna Turaka, MD, [2]Tianyu Li, MS, [5]Jian Q. Yu, MD, FRCPC,
[1]Nicos Nicolaou, MD, [3]Barbara Burtness, MD, [4]Miriam N. Lango, MD,
[4]John A. Ridge, MD, FACS., and [1]Steven J. Feigenberg, MD*

[1]Departments of Radiation Oncology, [2]Biostatistics,
[3]Medical Oncology, [4]Surgical Oncology, and 5Nuclear Medicine.
Fox Chase Cancer Center, Philadelphia, PA.,
*University of Maryland, Baltimore, MD.

**Corresponding Author:* Steven. J. Feigenberg, MD
Clinical Research Director, Department of Radiation Oncology
University of Maryland, Baltimore, MD 21201
Tel: 410-328-2326 Fax: 410-328-0691 email: sfeigenberg@umm.edu

Abstract. Objective: To evaluate outcomes and toxicities in patients with thyroid cancer treated with intensity-modulated radiation therapy (IMRT). **Methods:** This was a single institution retrospective review of 10 patients with thyroid cancer treated with IMRT at Fox Chase Cancer Center between May 2001 and June 2008. The median age was 69 years. Among the 10 patients, seven had papillary carcinoma, two had T3 and 8 had T4 disease, eight had N1 disease, and two had distant metastases. Radioactive iodine was given to all patients, while the median radiotherapy (RT) dose was 60 Gy. **Results:** Median follow up was 28.5 months (range: 4.5-to-50.6 months). The Kaplan-Meier estimates of 3-year local control, locoregional control, and overall survival rates 90%, 90%, and 80%, respectively. Nine patients had grade 2 skin toxicity, 10 had grade 2 pharyngitis/esophagitis, 2 had grade 2 laryngitis, and 3 had grade 3 laryngitis. Few grade 2 or 3 late toxicities were observed. **Conclusions:** IMRT is effective in the postoperative setting for the postoperative treatment of thyroid cancer. Long-term follow-up is still needed to assess the incidence of late toxicities.

Keywords • IMRT • Thyroid cancer • Radio-iodine therapy • RT toxicities

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Clinical and Laboratory Studies

Osteoporosis in Patients with Subclinical Hypothyroidism Treated with Thyroid Hormone Replacement

Pedro J. Tárraga López,[1] Francisco Naharro de Mora,[2]
José Antonio Rodríguez Montes,[3] Juan Solera Albero,[4]
Antonio Naharro Mañez,[5] Mª Carmen Frias López[6]

[1]General Practitioner, Centro de Salud 5 de Albacete and
Associate Professor of Medicine, Universidad de Castilla la Mancha
[2]General Practitioner, Centro de Salud 6 de Albacete
[3]Professor of Surgery, Universidad Autónoma de Madrid
[4]General Practitioner, Centro de Salud 7 de Albacete and
Associate Professor of Medicine, Universidad de Castilla la Mancha
[5]General Practitioner, Centro de Salud Alcadozo (Albacete)
[6]General Practitioner, Centro Salud Zona 4 Albacete

Corresponding Author: Dr. Pedro J. Tarraga López.
Calle Angel 53.1E. Albacete 02002. Spain
Tel: 34967505263. Fax: 34967225533, Email: pedrojuan.tarraga@uclm.es

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***Abstract*. Objective**: To estimate the prevalence of osteoporosis in patients being treated with thyroid hormone. **Method**: Cross-sectional retrospective study of primary care patients. Experimental Group: 112 patients diagnosed with subclinical hypothyroidism receiving thyroid hormone replacement therapy. Control Group: 70 subclinical hypothyroid patients not receiving thyroid replacement therapy. Once the sample was selected its members completed a clinical questionnaire and underwent a bone density scan with a validated measuring device. **Results**: Among the 182 patients studied, respectively, the experimental groups' mean age at diagnosis was 42.5 and the control patients' was 41.2 years; 32.7% were smokers as opposed to 33.2%; the coexistence of two or more cardiovascular risk factors were detected in 5.7% of experimental patients as opposed to ?% of control patients; mean TSH was 6.67 mU/L and mean free T4 was 1.04 ng/dL, compared to 5.95 mU/L and 0.98 ng/dL. The experimental and control groups significantly differed in percentage of reduced bone mineral density: respectively, 67% vs 35% lost bone mass, 86% vs 54% osteopenia, and 14% vas 5% osteoporosis. Fifty-six percentage of patients with bone loss were women. Control patients use no thyroid therapy for any time; in contrast, 72% of experimental patients used 100 or more mcg of T_4 and 12% use 150 mcg/day or more. Duration of T_4 treatment was 1-to-10 years for 61.1% of the patients and 10 years or more for 19.5%. **Conclusions**: The data used in this study indicate a high prevalence of bone loss in patients with subclinical hypothyroidism treated with exogenous thyroxine.

Keywords • Bone mass loss • Osteopenia • Osteoporosis • Subclinical hypothyroidism • Thyroxine replacement

Introduction

Osteoporosis is a skeletal disease characterized by reduced bone strength which predisposes to an increased risk of fracture. Bone strength is primarily a function of bone density and quality. Bone density is expressed as grams of mineral per area or volume and in any given individual is determined by peak bone mass and the amount of bone loss. Bone quality refers to macro- and micro-architecture, bone turnover, size, accumulated damage (e.g. microfractures), and mineralization.[10-15]

The definition of osteoporosis by the World Health Organization (WHO) is densitometric and non-clinical and is based on the measurement of bone mass with the DEXA method in the spine or hip. It establishes four categories: normal, osteopenia, osteoporosis, and established osteoporosis. The presence of pathological low bone mass, osteopenia or osteoporosis, is the best indicator of fracture risk for the region where the bone mass is measured; hence its interest, since bone loss is asymptomatic until it produces its natural consequence: the osteoporotic fracture.

Osteoporosis is a health issue with important implications for individuals, families, and the community. Untreated Osteoporosis results in unnecessary pain, restriction of function (disability), decreased quality of life, altered body image with low self-esteem, increased mortality, and serious economic consequences.[10-16]

In Spain it is estimated that osteoporosis causes 500,000 fractures a year and is responsible for 80,000 hospital stays. The annual incidence of hip fracture in patients over 50 years of age ranges between 2 and 3 per 1000, with a male/female ratio of 0:2 or 3:5. These are the injuries with the most serious social and health consequence. Acute phase mortality in hospitalized patients ranges from 5% to 8%, a figure that rises to between 20% and 30% in the first year. It is estimated that among survivors, only a third return to their independent status prior to the fracture. One third will require home care, and the remaining third will depend on chronic care centers.[12-18]

Moreover, 1-to-5 five women over the age of 50 have a spinal fracture. Some fractures are asymptomatic and related mortality is low, but some fractures produce chronic pain, height loss, respiratory problems, constipation, and abdominal pain. These symptoms limit the activity and quality of life of the patients.[12-21]

Primary care is the optimum mode of care for the prevention, diagnosis, and care of the osteoporotic patient. This view has been confirmed by organizations as prestigious as the National Osteoporosis Foundation.[16] Primary care is optimum for several reasons: the high prevalence and easy deployment of the available therapeutic arsenal and the characteristics of primary care relating to patient accessibility, and early diagnosis and treatment compliance. There exists, of course, criteria for referral of cases that require the patient to have other levels of care. These criteria will be addressed in this paper.

The generally-accepted definition of subclinical hypothyroidism is a condition of mild thyroid failure characterized by reference range levels of T_3 and T_4 and moderately elevated serum TSH. Although what constitutes an elevated TSH level is debated and varies from country-to-country, the upper limit of the TSH range we used in this study is between 5 and 10 mU/L.[1,2]

Increased access to serological tests for TSH have resulted in an increase in the number of patients as having abnormal thyroid function, although some patients are free from symptoms of the abnormality. This has led to a series of disputes among experts regarding the management and diagnosis of these patients.[3]

Subclinical hypothyroidism is a common condition, especially in middle aged and older adults. Its reported prevalence is between 3.9% and 6.5% in studies conducted in the United States[4,5] and 5.6% in Chile.[6] It is twice as frequent among women as men and three times more frequent among white people.[6]

Studies have shown that 30% of patients with subclinical hypothyroidism developed hypothyroidism within 10 years, and only 4% of patients with subclinical hypothyroidism normalized their TSH values. Factors that influence the progress of hypothyroidism are levels of TSH and the presence of antimicrosomal (thyroperoxidase) antibodies.[7] No studies we are aware of have shown a reduction in mortality among patients with subclinical hypothyroidism who were treated with thyroid hormone. With regard to the general symptoms of hypothyroidism, cohort studies have shown no significant difference in the presence of constipation, fatigue, or lack of energy in euthyroid patients and subclinical hypothyroid patients.[9]

Some authors have suggested that treatment of subclinical hypothyroidism with levothyroxine (thyroxine or T_4) may cause long-term osteoporosis. However, there is no evidence to support this theory, and studies have shown no difference in bone density or fracture risk in treated patients.[18,19]

A century ago, Von Recklinghausen described the thyrotoxicosis of bone due to hyperthyroidism. Hyperthyroidism is one of the endocrine diseases classically associated with osteoporosis.[36] The effect of hyperthyroidism on bone remodeling and metabolism has been thoroughly described. Mundy and his collaborators[37] found in 1977 that T_4 and T_3 can directly stimulate bone resorption *in vitro*. In addition, the normal bone remodeling cycle was reduced from 200 to 113 days. The remodeling was mainly at the expense of the formation period with a failure to replenish sufficient bone. Both formation markers of bone resorption may be elevated.

Patients with endogenous hyperthyroidism have reduced bone mineral density compared with euthyroid controls. It has been shown that treatment with exogenous thyroid hormone produced a significant increase in trabecular bone mineral density.[15]

Exogenous administration of suppressive doses of thyroxine may have a negative effect on bone mineral density. Diamond et al. found a decrease in femoral neck bone mineral density in pre- and post-menopausal women with thyroid carcinoma treated with suppressive doses of thyroxine; the reduction in lumbar spine bone mineral density was significant only in post-menopausal women.[5,8] Other controlled studies show no changes in bone mineral density with suppressive therapy.[15,19]

Based on the studies we described above, we decided to estimate the prevalence of osteoporosis in patients treated with thyroid hormone, considering such factors as doses of thyroxine and TSH levels. We also considered the time length of treatment.

Methods

This study was a retrospective cross-sectional evaluation of primary care patients. Patients were collected randomly and consecutively with an assumed confidence rate of 95%. The study sample consisted of a total 182 patients, 112 in the experimental group and 70 in the control group. The range was 14 to 65 years. All patients had to meet the laboratory criteria for subclinical hypothyroidism: They had to have a TSH level of at least 4.5 mU/mL and a free T_4 level within the reference range (0.8-1.2 ng/dL). Patients who were being treated with thyroxine replacement from June 2005 to January 2006 were included in the experimental group, and those who had not been treated with thyroid hormone were included in the control group.

Patients were analyzed for anthropometric variables, family and personal history, CBC, biochemistry, thyroid status, and treatment or non-treatment with thyroid hormone. Once the patient sample was selected, its members were summoned to complete a clinical questionnaire and undergo a bone density scan with a validated measuring device.

Of the 182 patients included, respectively, the experimental groups' mean age at diagnosis was 42.5 and the control patients' was 41.2 years. Among the experimental patients, 32.7% were smokers; 33.2% of control patients were smokers. Experimental and control patients had the coexistence of two or more cardiovascular risk factors. The mean TSH of experimental patients was 6.67 mU/L, and that of control patient was 5.95 mU/L. The mean free T_4 of experimental patients was 1.04 ng/dL and that of control patients was 0.98 ng/dL.

Statical Analysis. The description of qualitative data was done in absolute frequencies and percentages, and the quantitative data as means, standard deviations, median, minimum, and maximum.

Table 1. General Data

Variables	Experimental	Control
Age	42.5	41.2
Sex	88.5% women	81.5% women
Smokers	32.70%	33.20%
No cardiovascular risk factors	81.20%	80.30%
Diabetes	2.80%	2.50%
Hypertension	5.70%	5.10%
Variables	experimental	control
Lipid disorders	1.90%	1.50%
Variables	experimental	control
Body mass index	25.67	24.76
Systolic arterial pressure	119.75	115
Dystolic arterial pressure	71.86	70.5
Glycemia	87.71	90
Total cholesterol	193.92	195
TSH	6.67	5.95
T_4	1.09	0.98
CVR score	< 5%	< 5%

In the comparison of qualitative data between groups we used the Chi-square test and contingency tables by rearranging the percentages of several variables (TSH, total cholesterol, HDL-C, LDL-c).

Results

The experimental and control groups significantly differed in their mean percentages of reduced bone mineral density: respectively, lost bone mass (67% vs 35%), osteopenia (86% vs 54%), and osteoporosis (14% vs 5%). Among those with bone loss, 56% were women.

Control patients used no thyroid hormone therapy for any time; in contrast, 72% of experimental patients used 100 mcg/day or more mcg of T_4 and 12% used 150 mcg/day or more. Duration of the use of T_4 therapy was 1-to-10 years for 61.1% of the patients and 10 years or more for 19.5%.

Table 2. Treatment data.

Variables	Experimental	Control
Dose	72% 100 mg or more	0
Years of treatment	61.1% = 5-to-10	0

No statistically significant associations were found between TSH and the body mass index (BMI). The majority of patients had a normal BMIs (up to 25), independently of their TSH values.

As has already been mentioned, if it is estimated that there were 1040 consultations in this period it suggests that there would be an incidence of about 5% of new cases over a period of 6 months.

Patients presented with the following symptoms, which eventually led to diagnosis:

- Weight change (3.8%)
- Gynecological reasons (11.5%)
- Symptoms of depression (5.8%)
- Alopecia (5.8%)
- Musculoskeletal pains (11.5%)
- Non-specific fatigue-dizziness (30.8%)

Among the subjects studied 32.7% of the experimental group and 33.2% of the control group were smokers.

The association obtained between sex and TSH is close to being statistically significant in both groups with $p = 0.08$. For this reason we may assume that sex is a variable which may be dependent on TSH. In fact, when we look at the data obtained we can see that TSH is not distributed equally between the sexes but rather is predominant among women, regardless of the TSH range with which we are concerned. It remains the case, however, that 88.5% of the participants in the study were women.

With regard to the association between TSH and age, statistical significance was obtained ($p = 0.005$). We may thus assume that TSH is a variable dependent on age. It must be remembered, however, that the subjects of this study were relatively young, with an average age of 42.4 years.

With regard to the association between TSH and cholesterol (estimated for two ranges, one to 220 mg/dL and another > 20 mg/dL) a figure close to statistical significance was found in both groups; $p = 0.056$.

It should be pointed out that a relationship close to statistical significance, $p = 0.08$, was found between high TSH and a raised level of LDL and triglycerides.

With regard to the association between TSH and fasting glucose, a predominance of unaltered fasting glucose (up to 110) was found, regardless of the TSH range and there was no statistically significant relationship found.

A statistically significant relationship was found between TSH and mean free T_4 ($p = 0.04$), thus verifying feedback mechanism that regulates thyroid physiology.

Table 3. Bone metabolism data.

Variables	Experimental	Control	*p* value
Bone mass loss	67%	35%	$p = 0.002$
Osteopenia	86%	54%	$p = 0.001$
Osteoporosis	14%	5%	$p = 0.001$

Regarding diastolic blood pressure levels; it was found to be less than 90 mm Hg in most patient ranges with their being a statistically significant relationship between altered TSH and normal diastolic blood pressure levels ($p < 0.05$). A similar result was produced in the case of systolic blood pressure with the bulk of patients having a lower level than 140 mm Hg, compared with those with higher values.

In regard to osteopenia and osteoporosis, there was a clearly significant difference in the experimental group both in terms of degree of bone mass loss, significantly related to sex ($p < 0.05$), and years of treatment for hypothyroidism ($p < 0.039$). Nevertheless, we found no significant relationship between the dose of thyroid hormone being taken and the levels of TSH or T_4.

A statistically significant relationship was observed between bone mass grade and Z score. This suggests that the latter is a good variable to use for diagnosis.

Discussion

Subclinical hypothyroidism is defined by experts as a condition of mild thyroid failure. The failure is characterized by T_3 and T_4 within their respective reference ranges, with moderately elevated serum TSH, such as 5-to-10 mU/L.[11,15]

In the US, in 2002, the American Academy of Clinical Biochemistry lowered the preferred upper end of the TSH to 2.5; in 2003, the American Association of Clinical Endocrinology lowered the upper limit to 3.03. Because the upper level of the reference range various in different countries, may be add to the end of the last sentence of your paragraph above the following? "The failure is characterized by reference range of T_3 and T_4 with moderately elevated serum TSH of between 5 and 10 mU/L,[11,15] although in other countries, the upper limit of the TSH reference range is lower.[35]

In analyzing our results, we see that among out study patients, "symptoms" of subclinical hypothyroidism may include weight changes, various gynecological issues (infertility and changes in the duration and amount of the cycle), depression, alopecia, musculoskeletal pain, nonspecific fatigue, and dizziness. Such symptoms provided the motivation for patients to present to our health centre requesting that we measure their TSH levels.

The prevalence of subclinical hypothyroidism among patients in our health zone is 5%. This percentage is consistent with the incidence reported in other studies.

At an appropriate dose, levothyroxine is a safe medicine and can restore euthyroidism. However, before treatment begins, a number of possible side effects must be considered. These include exacerbation of ischemic heart disease and production of acute adrenal insufficiency. Care must be taken to determine the appropriate dose for the individual patient, as an excess of levothyroxine may lead to decreased bone mineral density, the onset of atrial arrhythmias, and the precipitation of angina pectoris. No descriptions of such complications have arisen. However, for precautionary purposes, patients with coronary artery disease should initially receive a lower dose of levothyroxine, usually 12.5-to-25 mg per day. This dose should be reassessed in 4-to-6 weeks, depending on both successive clinical assessments and determinations of TSH.

For patients with subclinical hypothyroidism (elevated TSH and in-range T_4) who have coronary artery disease, urgent or semi-elective surgery or invasive methods should not be delayed. The reason is that there is no evidence of increased risk of complications or mortality, even in cases of established hypothyroidism.[16-18]

The relationship between bone mass and thyroid functional status is an issue of utmost importance and current controversy. Thyroid hormones are essential for growth and development during childhood and for the maintenance of bone in adulthood. In hypothyroid children, physicians are likely to stunted growth with epiphyseal dysgenesis and delayed skeletal maturation. In adults, the phases of bone renewal are prolonged with reduced osteoblast activity and increased cortical bone thickness.[38]

However, the most pronounced effects of thyroid hormones on bone in adults are seen in hyperthyroidism. Hyperthyroidism is a common pathology, with a prevalence of 2% in women and 0.2% in men. Despite treatment, in the long term, the mortality rate increases in the female population to 2.9% as a result of the aftermath of femoral neck fractures.[20]

In a review of the impact of hyperthyroidism on bone, it was noted that 8% of patients had symptomatic bone disease. All of these patients were women and most were postmenopausal. Of these patients, 65% had severe bone pain or evidence of fractures, and up to 75% had been thyrotoxic for less than 1 year.[18,31]

The pathogenic mechanism that affects bone in hyperthyroidism is the increase both in the number and rate of bone turnover units. Thus, there is an increase in osteoclast and osteoblast activity. This reduces the remodeling cycle time by 50% and increases the frequency of activation of turnover units. These changes lead to an uncoupling between resorption and formation. The net result of the uncoupling is a loss of mineralized bone in varying amounts depending on factors such as sex, menstrual function, thyroid disease severity, and the sum of other risk factors for osteoporosis.[31-35]

At present there is little doubt about the deleterious effect of hyperthyroidism on bone. But controversy persists in two situations we will discuss in more detail because of their frequency and clinical implications: subclinical hyperthyroidism and chronic treatment with thyroid hormone.

Technical improvements have allowed progressively more sensitive measurements of the levels of TSH. Arguably, the TSH level is a reliable indicator of the tissue activity of the thyroid hormone. If so, and TSH levels are suppressed, even with thyroid hormone levels within their reference ranges, we can say that there exists a degree of tissue hyperthyroidism, a clinical condition known as subclinical hyperthyroidism. The condition has a prevalence of 1%, progressing to frank hyperthyroidism in approximately 5% of cases each year.

The loss of bone mass resulting from hyperthyroidism is only partially reversible.[32] Because of this, it seems logical that we should treat the condition as soon as possible, if it is shown that the condition is altering the bone metabolism. The controversy persists because early work showed that there was an increase of bone turnover in subclinical hyperthyroidism. In a recent study, however, tests run for correlations between TSH and bone mineral density were performed during follow-up periods of 4 to 6 years. These tests failed to demonstrate any difference between the groups with suppressed, normal, or high TSH levels.[31-35] In another study, patients who were treated to maintain euthyroidism had preserved bone density in the spine and hip, whereas untreated patients suffered a 2% annual decline in bone density.[35]

Despite the controversy, the most prevalent trend today is to treat subclinical hyperthyroidism early. Early treatment is warranted due to the possible potential impact of subclinical hyperthyroidism on bone, but also because of the cardiovascular risks it brings, such as an increased incidence of atrial fibrillation arrhythmias.[25]

Chronic treatment with thyroid hormones and its relationship to osteoporosis, the objective of this study, is one of the areas in which most work has been done in recent years. Here we must focus on two clearly different therapeutic objectives: suppressive treatment with thyroid hormones (with the objective of suppressing TSH levels, for example, in the treatment after surgery and radioiodine in differentiated thyroid carcinomas) and replacement therapy (with the goal of maintaining in-range TSH levels, used in primary autoimmune hypothyroidism).

With suppressive therapy the patient is maintained in a state of subclinical hyperthyroidism, showing in most studies an increased bone turnover. A recent meta-analysis included 1,250 patients from 41 studies. Study patients were stratified according to sex, menopausal status, dose of thyroid hormone, and anatomical sites in which densitometry was carried out, and exclusion of those who had previous hyperthyroidism, concluded that suppressive treatment caused a significant loss of bone mass in the lumbar spine and hip in postmenopausal women only, with an more pronounced effect in the cortical bone. The loss was less than 1 standard deviation on average: 7% in lumbar spine, 5% in femoral neck, 9% in Ward's triangle, and 7% in the distal portion of the radius.[29] These results should be regarded with caution and confirmed with controlled studies to look at both bone density and the incidence of fractures.

It has been shown that replacement therapy for Hashimoto's thyroiditis has no deleterious effects on bone. However, during long-term TSH-suppressive therapy, it is necessary to properly monitor TSH levels when it is absolutely necessary, as in high risk follicular thyroid carcinomas. The risks and benefits should be carefully considered in patients treated with suppressive doses of thyroxine therapy for thyroid nodular disease.[34,35] Exogenous administration of suppressive doses of thyroxine may have a negative effect on bone mineral density. Diamond and colleagues found a decrease in femoral neck bone mineral density in pre-and postmenopausal women with thyroid carcinoma treated with suppressive doses of thyroxine. However, reduction in lumbar spine bone mineral density was statistically significant only in postmenopausal women.[35]

Other controlled studies show no significant changes in bone mineral density with suppressive therapy. Such factors as the dose of thyroxine and level of TSH should be considered in analyzing these studies with conflicting results, while also taking into account issues related to the research design.[11,15]

In our study we observed a high prevalence of bone loss in patients treated with thyroxine. The bone loss was not related to the number of years the patients had been taking the hormone. This clearly leads to the decision that we must be cautious in starting treatment of a particular patient. Although subclinical hypothyroidism occurs in young people, we believe they should be treated only when it is necessary to do so.

Currently, no clinical practice guidelines recommend the use of exogenous thyroid hormone as a treatment for osteoporosis. In view of the results of the present study, consideration should be given to periodic bone mineral density testing to determine safe dosage levels for subclinical hypothyroid patients.

In the light of the widely variable study results we have cited, there is obviously a future need for more extensive study of subclinical hypothyroidism. Further studies are needed to determine the relationships of subclinical hypothyroidism to with other conditions. The studies are also important to determine whether patients would benefit from early treatment, not only in related to cardiovascular risk, but also to the prevention of osteoporosis and mood disorders.

Given the association of subclinical hypothyroidism with lipid abnormalities, other research considerations are also important. We need to more accurately assess the likelihood of an association with the probability of cardiovascular events. It may be, for example, that starting thyroid hormone therapy decreases the incidence of such events compared to untreated patients. If early treatment turns out to decrease the incidents of such events, it may eventually be established as a standard preventive measure.

To Treat or Not to Treat. At the end of the first decade of the third millennium, the controversy continues over the need to treat mild hypothyroidism, known as subclinical hypothyroidism. Those who treat with substitution therapy claim that it can deal with some symptoms that may be due to thyroid failure, prevent the condition advancing to overt hyperthyroidism, and produce cardiovascular benefits. Although theoretically treatment may prevent progression to overt hypothyroidism, improve a patient's lipid profile (and hence cardiovascular mortality), and improve symptoms, no studies of sufficient quality to prove this exists.

Once the diagnosis is made, an individual evaluation of the patient must be made. A reasonable framework for action is the following. Substitution treatment is indicated for:

- Depression, especially severe depression or depression that resists treatment.
- Pregnancy. Due to the adverse effects of hypothyroidism on fetal neurodevelopment, survival of the fetus, and its association with toxemia and gestational hypertension.
- Children, so as not to interfere with their growth and development.
- Hyperthyroidism of certain causes, including autoimmunity, post-I^{131}, post external radiotherapy, and post partial thyroidectomy.
- TSH > 10 mU/L.
- Goiter
- Symptoms, such as fatigue or cognitive deficits, and test results such as dyslipidemia, with testing performed 3-to-6 months.

Doubts exist about the benefits of treatment in cases of:

- Ischemic heart disease, although for some authors, the doses used are not contraindicated.
- Arrhythmias.
- Osteoporosis.
- Patients over 60 years, especially those over 85 years, in which subclinical hypothyroidism are associated with longevity.

Some authors[25-34] have suggested that treatment with levothyroxine may cause long-term osteoporosis, but there is no evidence to support this theory. Moreover, studies have shown no reduction in bone density or increased fracture risk in patients undergoing treatment.

In our study we saw that there a significant loss of bone mass that occurred with age. This leads us to four probable conclusions: (1) replacement therapy seems necessary, but (2) must start when hypothyroidism is confirmed, and (3) once treatment has begun, both the thyroid hormone and the loss of bone mass must be monitored so that treatment to impede bone loss can be begun if necessary. Therefore, (4) the multiplicity and the possible improvement of cardiovascular abnormalities associated with subclinical hypothyroidism suggest that the decision to treat a patient should depend on the presence of risk factors, rather than a threshold TSH level. Furthermore, (5) replacement therapy is with levothyroxine generally safe if excessive administration is avoided, and the treatment can be suspended if there is no clear benefit from its use. Treatment decisions can be made based on monitoring by serum levels of TSH.

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The Impact of Diabetes on Thyroid Dysfunction and Outcomes in a Native Indian Female Population

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Nima V. Thakkar, PhD and Sunita M. Jain, PhD

Department of Pharmacology, L.M.,
College of Pharmacy, Ahmedabad-380009, Gujarat, India

Corresponding Author: Dr. Nima Thakkar
Postal Address: Department of Pharmacology, L.M.
College of Pharmacy, Gujarat University, Navarangpura, Ahmedabad. 380009
Facsimile number: +91-9769995520 E-mail Address: neema149@gmail.com

***Abstract*. Introduction**: In the present study, the prevalence and pattern of thyroid dysfunction in an Indian female population with type 2 diabetes mellitus (T2D) were assessed. The aim was to find the correlation and comparison between these two major metabolic disorders. **Methods**: The study was a population-based survey of the prevalence of thyroid dysfunction in the T2D population. Participants in the study were 137 eligible females aged between 30-to-70 years. The biochemical parameters were body mass index (BMI), glycemic control (fasting and post prandial blood glucose levels, glycated haemoglobin A1c), and a thyroid profile (TSH, free T3, and free T4). These parameters were measured and compared with the normal population. Medication compliance was also considered. **Results**: Patients taking medications for both the conditions (T2D and hypothyroidism[HO]) showed controlled biochemical investigations compared to patients suffering from individual disorders; patients with both disorders had therapeutic stability. **Conclusion**: This study suggests that in the female population, T2D and HO are prevalent both individually and jointly. Further, there seems to be a good comparison between patients who have one of the metabolic disorders and those who have only one of them. The significant correlation positive between insulin use by T2D patients and disease complications was positive, and the correlation between hyperthyroidism and BMI was significantly negative. Age positively correlated with HbA1c and T2D duration. A significant correlation between T2D and HO was not established in this study. However, unsuspected/undiagnosed HO may be a matter of consideration for T2D patients.

Keywords • type 2 diabetes • hypothyroidism • metabolic disorder • prevalence • body mass index

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Clinical and Laboratory Studies

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Nima V. Thakkar and Sunita M. Jain

Department of Pharmacology, L.M.,
College of Pharmacy, Ahmedabad-380009, Gujarat, India.

Corresponding Author: Dr. Nima Thakkar
Postal Address: Department of Pharmacology, L.M.
College of Pharmacy, Gujarat University, Navarangpura, Ahmedabad. 380009
Facsimile number: +91-9769995520 E-mail Address: neema149@gmail.com

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Introduction

Type 2 diabetes (T2D) accounts for most individuals with non-autoimmune forms of diabetes. The spectacular increase in the prevalence of T2D worldwide is well documented.[1] Early identification is an important tool for the management of diabetes, as insulin resistance or relative insulin deficiency may lead to diverse complications of diabetes.[2]

Thyroid hormones play an indispensable role in various metabolic processes in the human body.[3] Hypothyroidism and hyperthyroidism are the main clinical conditions that affect the basal metabolic rate. Thyroid immunity is known to be more common in the female population. The higher incidence among females may be attributed to inhibition of disease activity by androgens and exacerbation by estrogens.[4,5]

Diabetes mellitus and thyroid diseases are the two most common endocrinopathies seen in the adult population. Excess or deficiency of either insulin or thyroid hormones can result in functional abnormalities of one another, as both of them are closely involved in cellular metabolism.[6] Possibly, thence, diabetes and thyroid disorders have a propensity to appear together in patients.[7,8] Patients with T2D commonly display the symptoms of hypothyroidism, and symptoms of hyperthyroidism have been documented in patients with type 1 diabetes.[8,9] Since there may be a link between diabetes and thyroid diseases, the American Diabetes Association (ADA) has proposed that people with diabetes be checked for thyroid disorders.[10]

In the light of the above facts, our objectives were to find out the prevalence of thyroid dysfunction in a T2D female population. An effort was made to compare and correlate these two metabolic disorders by taking into consideration various biochemical parameters. Pharmacological treatment compliance in each group was studied to determine the stability in terms of change in dose or type of medication for each subject.

Materials and Methods

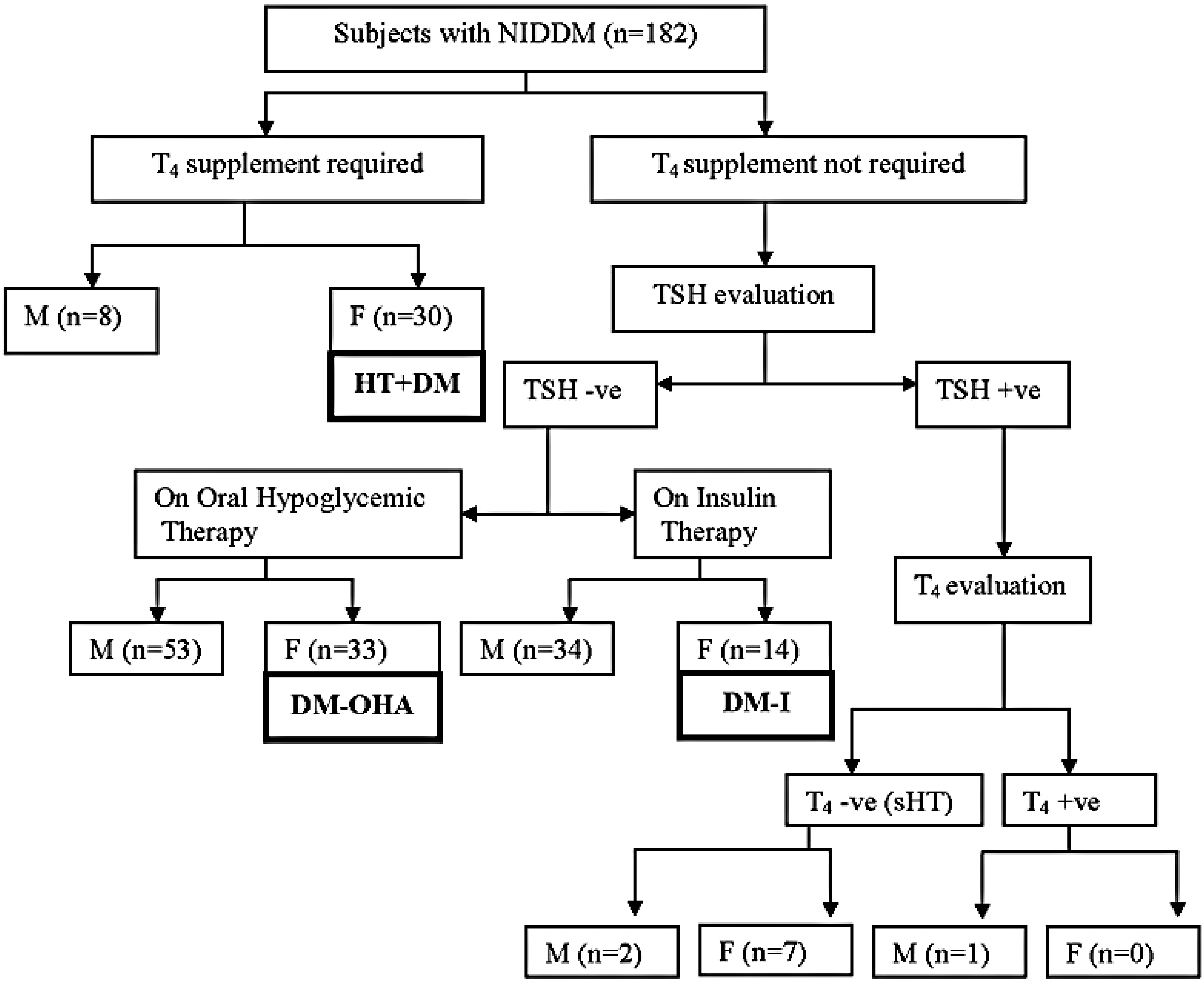
The protocol for the present study was approved by the human ethical committee of L.M. College of Pharmacy, Ahmedabad. All patients were given verbal and written information about the study prior to providing written consent.

A total of 182 female T2D patients were screened for thyroid dysfunction to find the prevalence of hypothyroidism and hyperthyroidism among them. Eligible for inclusion in the study were 77 female patients with a previously established diagnosis of T2D.

Patients were further grouped according to their pharmacological treatment. Thirty subjects were on both thyroxine therapy and diabetes medications. These 30 patients were classified as HT+DM. Thirty-three diabetes patients were on oral hypoglycemic agents, and 14 were on insulin therapy. These patients were classified as DM-OHA and DM-I, respectively.

Screening for Type 2 Diabetes

T4 = Thyroxine, M = male, F = female, sHT = subclinical hypothyroidism



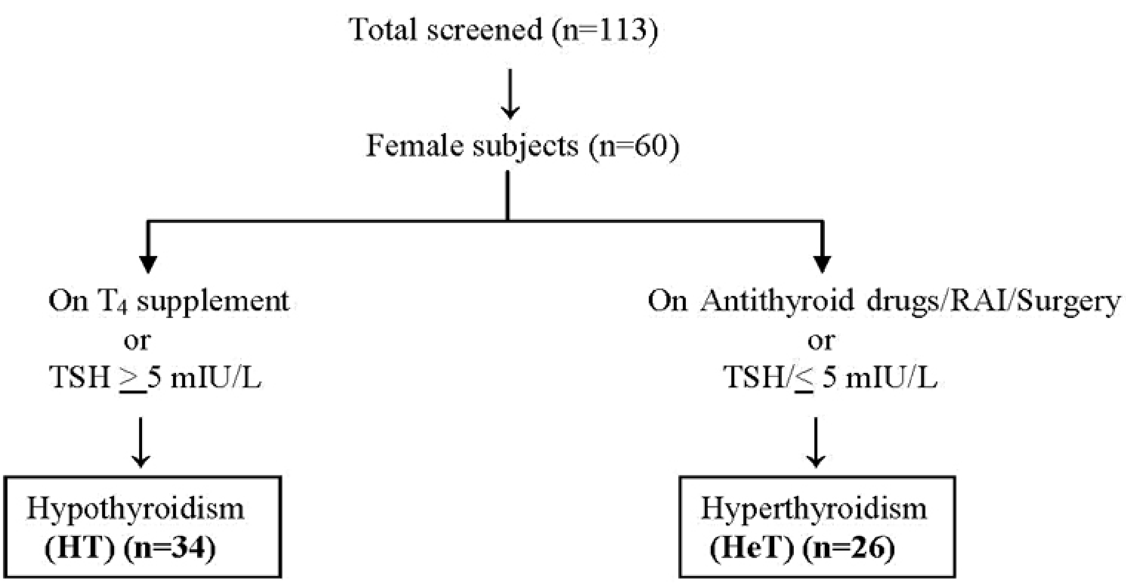
non-probability groups basis.

An effort was made to match groups of patients based on basic confounders like age, sex, and socioeconomic status. Diagnosis of disease condition(s) was required to have been established at least two years before a patient was admitted to the study. Patients were excluded if they had a history of ketoacidosis, impaired hepatic function, or severe anemias.

Pharmacological Treatment Compliance. Effectiveness of treatment was assessed at each study visit by detailed interviews of patients by the investigators, a probing questionnaire, and clinical and laboratory findings. Changes, if any, in prescription or worsening of diabetic and/or thyroid complications were assessed for each patient. A change in dose or type of medication was considered instability. Treatment was graded based on changes made at six-month intervals. Therapeutic stability was assessed by the grade for a total of two years of treatment. Medication compliance was assessed by counting the number of pills left and comparing the number with the number of pills scheduled the time of specified clinic visits.

Screening of Thyroid Dysfunction in Female Subjects

RAI = radioactive iodine



Baseline Characteristics. Baseline characteristics of all the subjects were composed by asking them to fill out the questionnaire pertaining to age, sex, years since disease condition(s) diagnosed, family history, complications associated with the disease(s), and food habits. Family history and complications were graded as per the stages of the disease(s) development.

Anthropometric Measurements. Body weight in light clothes was measured using a Krups weighing scale (Jammu & Kashmir, Srinagar, India) and height to the nearest 0.5 cm using portable stadiometers (Galaxy Scientific, New Delhi, India). Participants stood upright on a flat surface with the back of the heels and the occiput on the stadiometers. Body mass index (BMI) was calculated as the weight (in kilograms) divided by height squared (in meters).

Biochemical Investigations. Assessment of glycemic control (HbA1c, fasting, and post-prandial blood glucose [FPG and PPBS, respectively]) and thyroid profile [TSH, T_3, T_4 levels] were assessed at an interval of six months for two years prospectively.

All plasma levels were determined after a 10-hour overnight fast except PPBS, which was determined 2 hours after lunch. Venous blood samples were drawn from all patients between 08:00 and 09:00 hours. Plasma was obtained by the addition of Na-EDTA, 1 mg/mL, and centrifuged at 3000 g for

15 min at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at -80°C for ≤ 3 months. Plasma glucose levels were assayed by the hexokinase method (Shimadzu UV double beam spectrophotometer UV-1601, Columbia, USA). Glycated haemoglobin level (HbA1c) was measured by high-pressure liquid chromatography (HPLC) (Bio Rad D-10, Vadodara, Gujarat, India) techniques. Serum T_3, T_4, and TSH concentrations were estimated by enzymatic electrochemiluminescent immunoassay method (Abbott Architect i 2000, Abbott Laboratories, Abbott Park, USA).

Statistical Analysis. All the data are represented as mean ± SEM unless otherwise specified. One-way ANOVA followed by the Tukey-Kramer multiple comparison test was used to compare the data using Graph Pad Instat 3.01 software (La Jolla, CA, USA). Pearson product moment correlation was used to analyze the relationship between interdependence of laboratory findings in HT+DM subjects and Sigma Stat 2.03 (San Rafael, CA, USA) was used to correlate it. A value of $p < 0.05$ was considered as statistically significant.

Results

Pharmacological treatment for T2D subjects is shown below in Table 1: 74.8% of patients were on oral hypoglycemic agents, 28% were on insulin preparations, 72.9% were on statins, 38% were on fibrates, and 81% were on aspirin. Levothyroxine was take by 98.4% of subjects with hypothyroidism. Of the hyperthyroid patients, 86% were on thioamides, 54% were treated with radioactive iodine, and 2% had thyroid surgery. Two patients with hyperthyroidism were shifted to hypothyroidism and two with hypothyroidism were shifted to hyperthyroidism.

The average stability of patients complying with their therapy is demonstrated in Figures 1 & 2. Change in type or dose of medication was considered instability. It is clear from the graph that HT+DM subjects were found quiet stable (85% for anti-diabetes therapy and 92.9% for thyroid dysfunctioning therapy) as compared to individual in other groups, i.e. DM-OHA (68.8%), DM-I (58.9%), HT (56.6%), and HeT (45.2%) of patients.

Prevalence. Mean and standard error of mean were stratified by diabetic and/or thyroid dysfunctioning status. The incidence of thyroid dysfunctioning among T2D subjects (age 30-70 years) from the study community are presented in Table 1.

Table 1. Prevalence of thyroid dysfunctioning in T2D patients.

Gender	DM-OHA	DM-I	HT	HeT	HT+DM
Male n (%)	53 (61.18)	34 (70.83)	22 (39.29)	31 (54.39)	8 (21.05)
Female n (%)	33 (38.82)	14 (29.17)	34 (60.71)	26 (45.61)	30 (78.95)
Male / Female ratio	1.58	2.43	0.65	1.19	0.27

Values are number of subjects with percentage in parenthesis. DM-OHA = T2D subjects on oral hypoglycemic therapy, DM-I = T2D subjects on insulin therapy, HT = hypothyroid subjects, HeT = hyperthyroid subjects, HT+DM = subjects with hypothyroidism and T2D.

Among total screened 182 T2D subjects, 77 were female (42.31%), which were included into the study. As can be noted in the Table 1, the majority cases of HT+DM were found in females compared to males (30 vs. 8) reflecting female preponderance to be fairly high (78.95%) in HT+DM subjects.

Baseline characteristics. Baseline characteristics of randomized female subjects are presented in Table 2. BMI, a measure of obesity was associated with development of one or both metabolic disorders. BMI value of HT was incredibly high (31.8 kg/m^2), while HeT group had lower values (21.3 kg/m^2) when compared with the other groups. The age standardized prevalence rates of obesity (BMI) standardized prevalence rates of obesity (BMI) stratified by the presence of one or both metabolic disorders comparing the study population with the normal control female subjects has been presented in Figure 3.

As demonstrated in Figure 3, the burden of obesity was high in the study population, especially in hypothyroid females (82.4%). Higher incidences of diabetic secondary complications were eminent (22.34% higher) in DM-I group, which was statistically significant, when compared with the HT+DM subjects. On the other hand, lack of family history pervasiveness and minimal incidences of diabetes and/or thyroid complications were observed in HeT and HT+DM subjects, respectively (Table 2).

Glycemic control profile. As shown in Table 3, glycemic control in terms of FBS and PPBS, was found statistically significant in DM-OHA, DM-I

Table 2. Baseline characteristics of patients.

Groups	DM-OHA	DM-I	HT	HeT	HT+DM
Age (years)	57.21 ± 1.28	54.14 ± 2.36	47.74 ± 1.91	47.65 ± 1.66	50.77 ± 1.73
F (n%)	38.82	29.17	60.71	45.61	78.95
BMI (kg/m^2)	27.55 ± 0.99	28.52 ± 0.97	31.8 ± 1.15	21.25 ± 0.44*	29.99 ±1.01
Duration (years)					
DM	10.46 ± 1.81	13.57 ± 1.91	-	-	10.43 ± 1.42
TD	-	-	6.41 ± 0.55	3.88 ± 0.44	8.48 ±1.26
FH	1.13 ± 0.17	1.86 ± 0.31	2.00 ± 0.2	0.27 ± 0.09	1.59 ± 0.20
DC	1.33 ± 0.18	1.79 ± 0.28*	0.5 ± 0.096	0.85 ± 0.15	0.4 ± 0.15
FC (KCal)	1926.08 ± 86.13	48.21 ± 88.71 16	1922.55 ± 57.66	1570.46 ± 73.74	1844.46 ± 58.44

All the data are expressed as mean ± SEM. DM-OHA, DM-I, HT and HeT grouped data are compared with the HT+DM. whereby, *$p < 0.05$.

F = female, TD = thyroid disorder, FH = family History, DC = disease complications, FC = food calorie intake, DM-OHA = T2D subjects on oral hypoglycemic therapy, DM-I= T2D subjects on insulin therapy, HT= hypothyroid subjects, HeT= hyperthyroid patients, HT+DM = subjects with hypothyroidism and T2D.

and HT+DM group when compared with the normal group. group. However, rise in glucose levels was found clinically non-significant as these values were within the normal range (110-150 mg/dL). It was 112.5 and 153 mg/dl for FBS and PPBS respectively in HT+DM subjects. HbA1c, a major predictor of diabetes has been studied in all the groups. Although, it is very clear form our findings that HbA1c parameter did not change remarkably in the subjects having both T2D and HT complications (7.85%) as compared to individual groups viz., DM-OHA (9.08%) and DM-I (8.38%). The proportion of population showing HbA1c values higher than normal levels has been represented in Figure 4. As can be seen from graph, it is comparatively higher in diabetic subjects (DM-OHA and DM-I, 87.5% and 78.6% respectively) as compared to HT+DM subjects (73.3%).

Thyroid profile. Thyroid profile included measurements of T_3, T_4 and TSH levels. As can be seen in Table 3, T_3 and T_4 levels were significantly high in HeT subjects as compared to normal patients ($p < 0.05$). At the same time, these levels remained significantly low in HT subjects when compared with normal subjects. However, there was a remarkable increase in TSH levels ($p < 0.05$) observed in the HT group. TSH levels remained significantly low in HeT group subjects. HT+DM subjects showed almost normal thyroid profile values of compared to individual disease groups in the study. The percentage of subjects in each group whose TSH values were outside the reference range (0.5-4.0 mIU/L) are represented in Figure 5.

As shown in Figure 5, TSH levels were found above normal range in 56% population of HT subjects and 38% population showed below normal levels in HeT subjects. However, only 20% population of HT+DM group showed altered TSH values. Further, 33% DM-OHA subjects showed higher than normal values of TSH in a prospective study during their two years follow-up. However, the mean value lies within normal range, but overall TSH levels were slightly above than upper limits of TSH values (5 mIU/L).

In addition to above, as shown in Table 4, age, diabetes duration and HbA1c values showed positive correlation coefficients with *p* values below 0.05. They tend to increase together, revealing that age is a predisposing factor to diabetes mellitus.

Thus, the data demonstrate association of diabetes with thyroid dysfunction to a certain extent. It is particularly notable that simultaneous control of these two major metabolic disorders, namely T2D and thyroid dysfunction, is protective against diabetic complications.

Discussion

Therapy of each group was assessed retrospectively from records for two years. Also, therapeutic changes were noted in the patient population during the prospective designed study. Depending upon the grades provided for each therapy, grade changes were noted for data from the last two years. DM-OHA and DM-I subjects showed significant variation in antidiabetic therapy medication and dosage when compared with the HT+DM subjects. Similarly, HT and HeT subjects underwent a wide range of changes in therapy within two years' duration as compared to HT+DM subjects. These facts may possibly draw our attention towards a mutual role of thyroid and insulin hormones in governing and maintaining the status of the two diseases.

Table 3. Biochemical Investigations.

Parameter	Normal	DM-OHA	DM-I	HT	HeT	HT+DM
FBS (mg/dL)	85.8±1.75	130.08±6.37$^{\#\#}$	134.04±6.09$^{\#\#}$	92.9±2.24	89.04±3.72	112.5±12.6$^{\#\#}$
PPBS (mg/dL)	113.93±1.7	180.65±9.66$^{\#\#}$	168.73±9.54$^{\#\#}$	107±2.5	107.78±2.9	153±10.7$^{\#\#}$
HbA1c (%)	5.91±0.13	9.08±0.34$^{\#\#}$	8.38±0.44$^{\#\#}$	6.14±0.17	6.06±0.09	7.85±0.26$^{\#\#}$
TSH (mIU/L)	2.7±0.28	4.07±0.32	2.86±0.39	6.94±0.79**$^{\#}$	0.82±0.19	4.89±1.36
Serum T_3 (mIU/L)	4.47±0.32	1.55±0.38	1.41±0.34	1.49±0.3	31.11±10.0**	2.26±0.48
Serum T_4 (mIU/L)	24.89±13.42	8.24±0.92	9.02±0.69	9.09±0.39	16.93±1.08*	7.33±0.59

All results are expressed as Mean ± SEM.
DM-OHA, DM-I, HT and HeT grouped data are compared with the HT+DM. *p < 0.05, **p < 0.01.
DM-OHA, DM-I, HT, HeT and HT+DM grouped subjects were compared with the normal subjects' population.
#*p* < 0.05, ##*p* < 0.01, ###*p* < 0.001.
FBS = fasting blood sugar levels, PPBS = post-prandial blood sugar levels, HbA1c = glycated Haemoglobin A1c.
TSH= thyroid stimulating hormone, T3= Tri-iodo thyronine, T4= Thyroxine. DM-OHA= T2D subjects on oral hypoglycemic therapy, DM-I= T2D subjects on insulin therapy, HT= hypothyroid subjects, HeT= hyperthyroid subjects, HT + DM = subjects with hypothyroidism and T2D.

High prevalence rates of T2D and hypothyroidism have been reported in different populations,[11,12] but the full impact of the development of these two metabolic abnormalities appears to be evolving. The female predominance of developing T2D and thyroid dysfunction simultaneously is 78.95% (30 out of 38). This finding supports the higher-than-normal prevalence of these two major metabolic disorders at the same time in the female population.[8] This may also support the observation that thyroid autoimmunity is common in T2D female patients.[13] In the present study, we observed a high prevalence of both disorders together in the female population of Gujarat. Hypothyroidism was the more commonly observed thyroid dysfunction in HT+DM patients; hyperthyroidism developed in only one patient with T2D.

BMI, a major predictor of obesity,[14] was higher in the study population, except that of hyperthyroid subjects. Their lower BMI may have been due to increased metabolism in hyperthyroidism. Decreased basal metabolic rates (BMR) in hypothyroid subjects may also have been responsible for the increased BMI in this study population.

Nonetheless, obesity is a major risk factor for T2D and hypothyroidism.[15] It has been demonstrated in other studies that deterioration of glucose tolerance is associated with an increase in obesity for both the male and female population.[16] A strong positive family history observed in our study might have played an important role in the development of these hormonal metabolic disorders and supports the observations of other investigators.[17,18]

Development of secondary complications in diabetes was more common among the DM-OHA and DM-I subjects, as compared to HT+DM subjects. This leads to a thought that hypothyroidism may decrease insulin requirements and thereby protect against development of harmful consequences of diabetes.[19]

It is particularly notable that simultaneous control of these two metabolic disorders is beneficial in reducing glucose tolerance as evident by HbA1c values in this study population. In one case study, as thyroid hormone levels moved into the reference range, glycated albumin and glycated haemoglobin returned to their normal relative ratio after three months.[20] Our study also supports the report that HbA1c values are controlled in HT+DM patients.

Table 4. Interdependence of parameters in HT+DM subjects.

	Age	BMI	DM duration	TD duration	HbA1c	TSH
Age	1.00	-0.20 (0.298)	0.53 (0.00345)	0.05 (0.811)	0.67 (0.0000503)	-0.24 (0.212)
BMI		1.00	-0.27 (0.155)	0.13 (0.492)	-0.27 (0.143)	-0.15 (0.424)
DM duration			1.00	0.30 (0.114)	0.04 (0.828)	-0.08 (0.684)
TD duration				1.00	-0.13 (0.514)	-0.13 (0.494)
HbA1c					1.00	-0.25 (0.178)

Pearson correlation coefficient test was applied for HT+DM group. BMI = body mass Index, DM = T2D, TD = thyroid dysfunction, HbA1c = glycated hemoglobin A1c. All data are shown as correlation coefficients with *p* values in parenthesis. The pair of variables with positive correlation coefficients and *p* values below 0.050 tends to increase together. For the pairs with negative correlation coefficients and *p* values below 0.050, one variable tends to decrease while the other increases. For pairs with *p* values greater than 0.050, there is no significant relationship between the two variables.

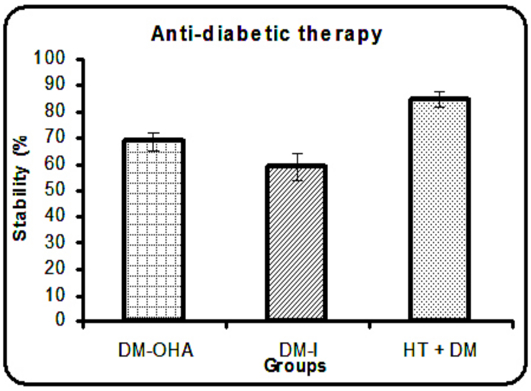


Figure 1. Stability of Anti-diabetic therapy in T2D population. All data are shown in its mean values. DM-OHA = T2D subjects on oral hypoglycemic therapy, DM-I = T2D subjects on insulin therapy, HT+DM = subjects with hypothyroidism and T2D.

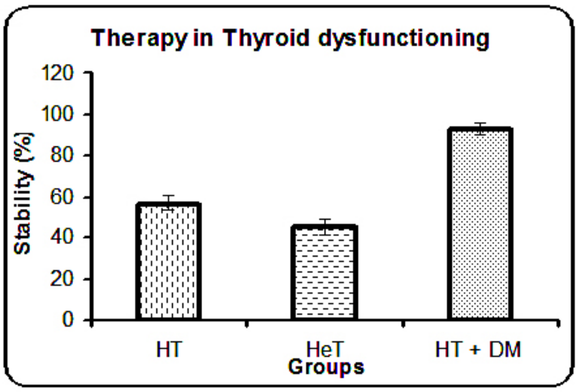


Figure 2. Stability of therapy in thyroid dysfunctional population. All data are shown in its mean values. HT = hypothyroid patients, HeT = hyperthyroid patients, HT+DM = subjects with hypothyroidism and T2D.

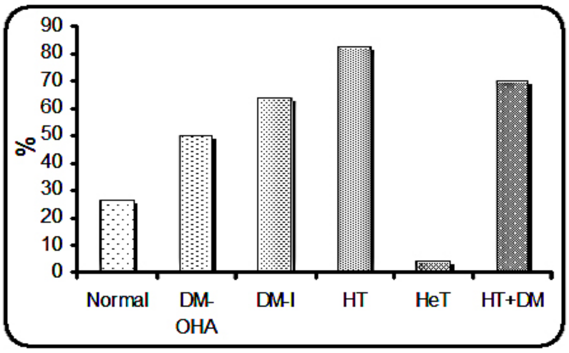


Figure 3. Prevalence (/100) of subjects with BMI >/= 27 kg/m^2. All the data are shown in its mean values. DM-OHA = T2D subjects on oral hypoglycemic therapy, DM-I = T2D patients on insulin therapy, HT = hypothyroid patients, HeT = hyperthyroid patients, HT+DM = subjects with hypothyroidism and T2D.

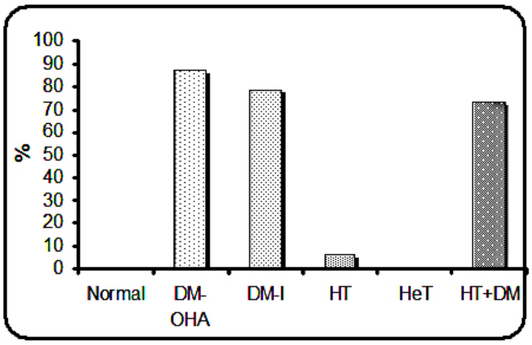


Figure 4. Proportion (/100) of subjects with HbA1c >/= 7%. All the data are shown in its mean values. DM-OHA = T2D subjects on oral hypoglycemic therapy, DM-I = T2D subjects on insulin therapy, HT = hypothyroid subjects, HeT = hyperthyroid subjects, HT+DM= subjects with hypothyroidism and T2D.

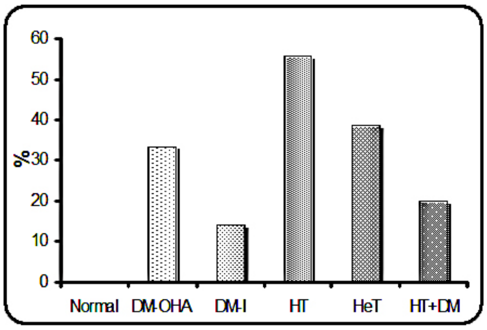


Figure 5. Prevalence (/100) of patients with TSH < 0.5 or > 5 mIU/L. All data are shown in its mean values. DM-OHA = T2D patients on oral hypoglycemic therapy, DM-I = T2D patients on insulin therapy, HT = hypothyroid patients, HeT = hyperthyroid patients, HT+DM = patients with hypothyroidism and T2D.

It has been speculated that serum T_3 levels, basal TSH levels, and the TSH response to thyrotropin releasing hormone (TRH) might be affected by the glycemic status of euthyroid individuals who have T2D[21,22]

In the present study, we observed higher TSH levels ($p < 0.05$) in diabetic subjects receiving oral hypoglycemic medications. Therefore, long-term usage of sulphonamides may lead to the development of hypothyroidism. It is possible, though, that an underlying mechanism could not be established at this point of time; blockade of K_{ATP} by sulphonylureas may reduce the Ca^{++} entry inside the cell and thereby slow down cellular metabolism and lead to conditions like hypothyroidism.[23]

In our study, we found that there is interdependence between insulin and thyroid hormone for normal cellular metabolism. It is apparent, then, that diabetes mellitus and thyroid diseases can mutually influence each other's pathological progress. In one study, after introduction of substitution therapy with levothyroxine, decreased insulin resistance was established.[24,25] Similarly, patients who have both disorders are relatively stable considering their diabetes and thyroid profiles. Thus, thyroid hormone therapy may reduce patients' complications associated with T2D.

Conclusion

Thyroid disorders are quite prevalent in female population of India. There appears to be a higher than normal occurrence of thyroid disorders in people with T2D, with hypothyroidism being the most common. An overactive role of thyroid gland may increase the insulin requirements, but an under active thyroid gland may decrease insulin requirements. Thus, there seems to be a good comparison between hypothyroidism and T2D patients. However, a significant correlation between them could not be established by our study. Further, it is suggested that unsuspected or undiagnosed subclinical hypothyroidism is likely to affect the diabetes status.

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Intensity Modulated Radiation Therapy (IMRT) for Thyroid Cancer

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[1]Aruna Turaka, MD, [2]Tianyu Li, MS, [5]Jian Q. Yu, MD, FRCPC,
[1]Nicos Nicolaou, MD, [3]Barbara Burtness, MD, [4]Miriam N. Lango, MD,
[4]John A. Ridge, MD, FACS., and [1]Steven J. Feigenberg, MD*

[1]Departments of Radiation Oncology, [2]Biostatistics,
[3]Medical Oncology, [4]Surgical Oncology, and 5Nuclear Medicine.
Fox Chase Cancer Center, Philadelphia, PA.,
*University of Maryland, Baltimore, MD.

**Corresponding Author:* Steven. J. Feigenberg, MD
Clinical Research Director, Department of Radiation Oncology
University of Maryland, Baltimore, MD 21201
Tel: 410-328-2326 Fax: 410-328-0691 email: sfeigenberg@umm.edu

Abstract. Objective: To evaluate outcomes and toxicities in patients with thyroid cancer treated with intensity-modulated radiation therapy (IMRT). **Methods:** This was a single institution retrospective review of 10 patients with thyroid cancer treated with IMRT at Fox Chase Cancer Center between May 2001 and June 2008. The median age was 69 years. Among the 10 patients, seven had papillary carcinoma, two had T3 and 8 had T4 disease, eight had N1 disease, and two had distant metastases. Radioactive iodine was given to all patients, while the median radiotherapy (RT) dose was 60 Gy. **Results:** Median follow up was 28.5 months (range: 4.5-to-50.6 months). The Kaplan-Meier estimates of 3-year local control, locoregional control, and overall survival rates 90%, 90%, and 80%, respectively. Nine patients had grade 2 skin toxicity, 10 had grade 2 pharyngitis/esophagitis, 2 had grade 2 laryngitis, and 3 had grade 3 laryngitis. Few grade 2 or 3 late toxicities were observed. **Conclusions:** IMRT is effective in the postoperative setting for the postoperative treatment of thyroid cancer. Long-term follow-up is still needed to assess the incidence of late toxicities.

Keywords • IMRT • Thyroid cancer • Radio-iodine therapy • RT toxicities

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Clinical and Laboratory Studies

Intensity Modulated Radiation Therapy (IMRT) for Thyroid Cancer

[1]Aruna Turaka, MD, [2]Tianyu Li, MS, [5]Jian Q. Yu, MD, FRCPC,
[1]Nicos Nicolaou, MD, [3]Barbara Burtness, MD, [4]Miriam N. Lango, MD,
[4]John A. Ridge, MD, FACS., and [1]Steven J. Feigenberg, MD*

[1]Departments of Radiation Oncology, [2]Biostatistics,
[3]Medical Oncology, [4]Surgical Oncology, and [5]Nuclear Medicine.
Fox Chase Cancer Center, Philadelphia, PA.,
*University of Maryland, Baltimore, MD.

Corresponding Author: *Steven. J. Feigenberg, MD
Clinical Research Director, Department of Radiation Oncology
University of Maryland, Baltimore, MD 21201
Tel: 410-328-2326 Fax: 410-328-0691 E-mail: sfeigenberg@umm.edu

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Abstract. **Objective:** To evaluate outcomes and toxicities in patients with thyroid cancer treated with intensity-modulated radiation therapy (IMRT). **Methods:** This was a single institution retrospective review of 10 patients with thyroid cancer treated with IMRT at Fox Chase Cancer Center between May 2001 and June 2008. The median age was 69 years. Among the 10 patients, seven had papillary carcinoma, two had T3 and 8 had T4 disease, eight had N1 disease, and two had distant metastases. Radioactive iodine was given to all patients, while the median radiotherapy (RT) dose was 60 Gy. **Results:** Median follow up was 28.5 months (range: 4.5-to-50.6 months). The Kaplan-Meier estimates of 3-year local control, locoregional control, and overall survival rates 90%, 90%, and 80%, respectively. Nine patients had grade 2 skin toxicity, 10 had grade 2 pharyngitis/esophagitis, 2 had grade 2 laryngitis, and 3 had grade 3 laryngitis. Few grade 2 or 3 late toxicities were observed. **Conclusions:** IMRT is effective in the postoperative setting for the postoperative treatment of thyroid cancer. Long-term follow-up is still needed to assess the incidence of late toxicities.

Keywords. • IMRT • Thyroid cancer • Radio-iodine therapy • RT toxicities

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Introduction

Surgical resection with or without radioactive iodine therapy (RAI) is the typical management of differentiated thyroid cancer. The role of external beam radiation therapy is controversial. The NCCN guidelines currently recommend postoperative radiation therapy (PORT) for T4 disease with extra-thyroidal extension and when the patient's age is more than 45 years. Local failures occur in the thyroid bed, the surrounding target volume, and regional lymph nodes. The irregular shape of this target volume and the wide extent of lymph node stations at risk mean that delivering doses beyond 50 Gy (5,000 rad) by conventional methods of radiation technique is difficult.

Intensity-modulated radiation therapy (IMRT) provides better dose coverage to the target volume.[1,2] To date, there is limited published data available with only 33 cases reported in the literature using IMRT[3-5] to treat thyroid cancer. We report the local control rates and toxicities in a series of 10 patients with thyroid cancer treated with IMRT at Fox Chase Cancer Center (FCCC).

Materials and Methods

The FCCC institutional review board approved this retrospective review. Between November 2002 and September 2007, 11 patients with thyroid cancer were treated at FCCC with IMRT. One patient was excluded from analysis because of the development of distant metastases during a course of radiation for an inoperable anaplastic thyroid carcinoma. Among the remaining patients, five were treated with postoperative radiation therapy (PORT) followed by

RAI, while five were treated with RAI then PORT (Table 1). PORT is recommended at FCCC for patients older than 60 years of age with T4 disease, extra thyroid extension, gross residual disease, and multiple positive lymph nodes with extra capsular extension.

Table 1. Study group characteristics (n = 10)

Variable (%)	Number. of patients
Age, median, in years (range)	69 (51-85)
< 70	4 (40)
≥ 70	6 (60)
Sex	
Male	5 (50)
Female	5 (50)
T stage	
T3	2 (20)
T4	8 (80)
N stage	
N0	2 (20)
N1	8 (80)
M stage	
M0	7 (70)
M1	3 (30)
Overall stage	
III	1 (10
IV A	6 (60)
IV B	0 (0)
IV C	3 (20)
III/ IV A	7 (70)
IV B/ C	3 (30)
Histology	
Papillary	7 (70)
Follicular	1 (10)
Insular	1 (10)
Anaplastic	1 (10)
Path size primary	
≤ 4 cm	7 (70)
≥ 4 cm	3 (30)
Multifocality	
Yes	4 (40)
No	6 (60)
Extrathyroid extension, positive	9 (90)
Type of surgery	
Subtotal thyroidectomy	2 (20)
Total thyroidectomy	8 (80)
Resection status	
Complete	5 (50)
Incomplete	5 (50)
Margin status	
Positive	10 (100)
Grade	
Well differentiated	5 (50)
Papillary with Tall cell features	2 (20)
Papillary with follicular features	1 (10)
Papillary with anaplastic features	1 (10)
Poorly differentiated	1 (10)
Neck dissection	
Yes	4 (40)
Lymph nodes (LN)	
Positive	8 (80)
≥ 2 LN positive	6 (60)
Extra nodal extension positive	1 (10)
Treatment details	
Sx +PORT + RAI	5 (50)
Sx + RAI + PORT	5 (50)
RAI dose (mCi) 10 (100)	
50-100	1 (10)
100-150	3 (30)
> 150	4 (40)
Missing dose details	2 (20)

Abbreviations: T = tumor, N = nodal stage, M = metastasis, cm = centi meters, % = percentage, Sx = surgery, PORT = postoperative radiation therapy, RAI = Radio-iodine ablation, mCi = milli Curies.

Radiotherapy. Patients were simulated using CT simulation with an Aquaplast mask (WFR/Aquaplast Corp, Avondale, PA) to improve daily reproducibility. Axial images were obtained every 3 mm from the top of the head to 5 cm below the carina. The treatment regions included the thyroid bed, levels II-to-VI lymph nodes, and the superior mediastinum lymph nodes.

IMRT was delivered with 7 or 8 fixed beams. The planning target volume (PTV) was prescribed to 60 Gy in 30 fractions, 2 Gy per fraction, one fraction per day. Normal tissue constraints were as follows: Spinal cord dose was limited to less than 45 Gy, brain stem to < 54 Gy, brachial plexus to < 62 Gy, and parotid glands limited to 26 Gy. The Corvus inverse treatment planning system was used for the majority of patients (version 3.0, NOMOS Corp., Cranberry Township, PA). For an ideal plan, 95% of PTV should receive 60 Gy with at least PTV getting 93% of the prescribed dose and hot spots should be less than 120%.

Table 2. Radiation therapy details (n = 10)

Variable	**Number. of patients (%)**
Type of treatment	
PORT	8 (80)
PORT + CT	2 (20)
RT dose (Gy)	
56	1 (10)
60	5 (50)
68	1 (10)
70	3 (30)
PTV1 in Gy, median, range	60 (56-70)
PTV2 in Gy, median, range	57 (40-70)
No of beams, median, range	7 (7-8)
No of fractions, median, range	32 (28-35)
RT duration in months, median, range	1.54 (1.22- 1.74)
Interval between surgery and RT, mo	3.45 (0.82-32.10)
Chemotherapy	
Yes	2 (20)
Doxorubicin based	2 (100)

Abbreviations: PTV1, 2 = planning target volume one and two, Gy = gray, PEG = percutaneous endoscopic gastrostomy, CT = chemotherapy, RT = radiation therapy.

Radio-iodine therapy. At FCCC, all patients were evaluated with ^{123}I scan postoperatively to assess for potential residual disease or residual normal thyroid tissue. For patients with residual disease/thyroid tissue, ^{131}I ablation was performed to eliminate tissue/disease and enable thyroglobulin monitoring for recurrence. The doses used were 100 mCi (milli Curies) to the thyroid bed and 150 mCi in the presence of positive lymph nodes. One hundred seventy-five mCi ^{131}I were administered for lung and 200 mCi for bone metastases. Thyroid hormonal suppression was instituted in all patients post-ablation.

Statistical analysis. Descriptive data of diagnostic and treatment factors were obtained for all patients. Three-year actuarial rates of overall local relapse free and local-regional relapse free survivals were obtained via Kaplan-Meier estimation method. All the analyses were performed using the statistical analysis systems (SAS institute, Cary, NC). Acute and late toxicity were recorded as per the Radiation Therapy Oncology Group6 (RTOG) toxicity criteria.

Results

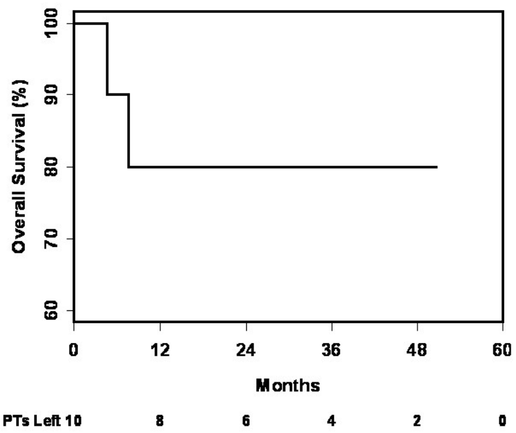
Median follow-up was 28.5 months (range: 4.5-to-50.6 months). Patient, tumor, and treatment-related characteristics are shown in Tables 1 and 6. Median age was 69 years (range: 51-to-85 years) with 4 patients ≥ 70 years old. There were 5 men and 5 women. Four patients had a prior history of goiter.

The histological pattern was papillary in 7 patients, follicular in 1, insular in 1, and anaplastic cancer in 1. There were 2 patients with stage T3 and 8 patients with stage T4. Eight patients had stage N1 and three presented with metastatic disease (stage IV C).

Subtotal thyroidectomies were performed in 2 patients and 8 underwent total thyroidectomies. Neck dissection (central compartment) was performed in 4 patients. Seven patients had tumor size ≤ 4 cm and multifocal disease was seen in 4 patients. Extrathyroid extension was seen in 9 patients and all 10 patients had positive margins. Six patients had > 2 lymph nodes positive at resection. None of the patients had gross residual disease. Among patients with papillary carcinoma, two had tall cell features, one had associated follicular, and one had anaplastic component. RAI was done in all patients with ^{123}I scans prior to ablation. All but one patient received > 100 mCi of ^{131}I .

The median dose to PTV was 60 Gy (range: 56-to-70 Gy) over a duration of 1.54 months (range: 1.22-to-1.74 months), 2 Gy per fraction, one fraction per day. The median-time between surgery and the initiation of radiation therapy (EBRT) was 3.45 months (range: 0.82- to-32.10 months, Table 2). Two patients were treated with concurrent chemotherapy with dox-

Figure 1: Overall survival rates for all 10 patients



orubicin 15 mg/m^2, weekly over 7 weeks during radiation therapy. Chemotherapy was given to a patient who had an anaplastic spindle cell carcinoma associated with a multifocal tall cell papillary thyroid carcinoma. Two of 3 lymph nodes were positive for metastatic disease. The second patient had high-grade multifocal papillary carcinoma with anaplastic features with 8 of 73 lymph nodes demonstrating metastatic disease.

Table 3. Incidence of grade 2 and 3 acute and late toxicities

	Grade 2, N (%)		Grade 3, N (%)	
	Acute	Late	Acute	Late
Skin	9 (90)	0 (0)	0 (0)	0 (0)
Mucosa	5 (50)	0 (0)	1 (10)	0 (0)
Pharynx/ Esophagitis	10 (100)	2 (20)	0 (0)	1 (10)
Larynx	2 (20)	2 (20)	3 (30)	0 (0)
Taste changes	6 (60)	—	0 (0)	—
Xerostomia	6 (60)	4 (40)	0 (0)	0 (0)
Hematological	1 (10)	0 (0)	0 (0)	0 (0)

Abbreviations: N = number of patients.

The Kaplan-Meier estimates of 3-year local and locoregional control rates were 90%, 90%, and the overall survival was 80% for all patients (shown in Figures 1, 2A, 3A). The distant metastasis free-rate was 87% at 1-year and 58% at 3-years. Only one patient had persistent disease 3 months following radiation therapy to 70 Gy. He was a 77-year-old male with poorly differentiated insular carcinoma treated with EBRT for local recurrence 3 years after surgery and RAI. One patient developed supraclavicular lymph node metastases (in-field failure). Two patients developed distant metastases. At last follow-up, 8 patients were alive and 2 were dead.

Figure 2A: Local control rates for all 10 patients

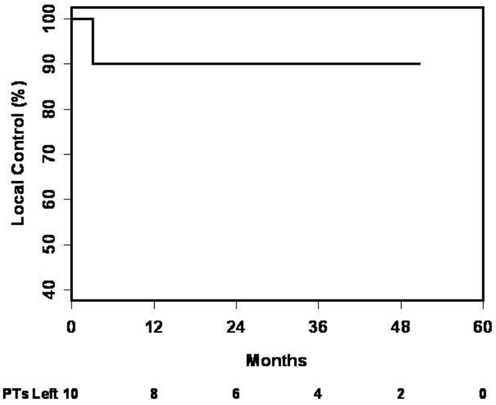
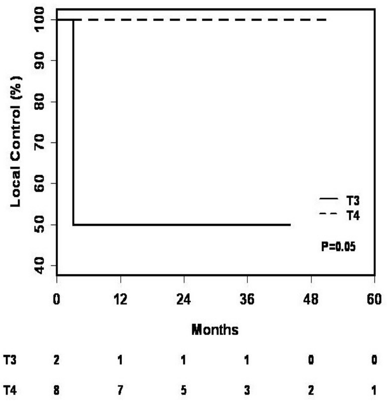


Figure 2B: Local control rates for all 10 patients based on T stage



On univariate analysis including age (< 70 versus > 70 years), gender (male versus female), N-stage (N0 versus N1), overall stage (III/IVa versus IV b/c), number of lymph nodes positive (< 2 versus > 2) or extra nodal extension (yes versus no) and addition of chemotherapy (yes versus no), only T stage (T3 versus T4) and type of surgery (partial versus total thyroidectomy) were significant for local failure (p = 0.05, 0.05, respectively Table 4, Figures 2B, 3B). Al-

Figure 2C: Local control rates for all 10 patients based on type of surgery

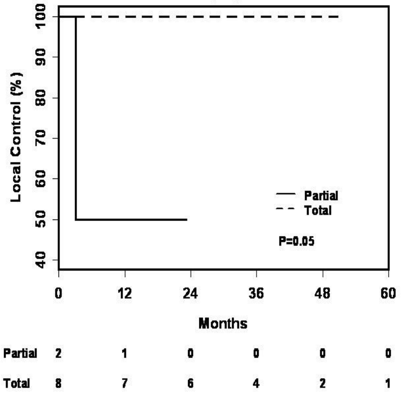


Table 4. Univariate analysis of variables on the clinical outcomes

Variable	OS*	**LC rate***	LRC rate*	DM free rate*
Age (<70 vs ≥ 70 years)	0.06	0.22	0.22	0.56
Gender (male vs. female)	0.94	0.32	1.00	0.81
T stage (T3 vs T4)	0.18	0.05	0.05	0.01
N stage (N0 vs N1)	0.46	0.62	0.64	0.52
M stage (M0 vs M1)	0.58	0.51	0.77	0.52
Overall stage (III/Iva vs IVb/c)	0.58	0.51	0.77	0.52
Type of surgery (subtotal vs total thyroidectomy)	0.18	0.05	0.05	0.71
Resection status (complete vs incomplete)	0.94	0.32	0.16	0.23
LN positive (< 2 vs ≥ 2)	0.23	0.41	0.89	0.81
Extra nodal extension (yes vs no)	0.63	0.74	0.30	0.35
Size of tumor (< 4 vs ≥ 4 cm)	0.44	0.13	0.13	0.08
Multifocality	0.23	0.41	0.41	0.32
Extra thyroid extension (yes vs no)	0.63	0.74	0.74	0.71
Chemotherapy (yes vs no)	0.46	0.62	0.62	0.36
Dose of I-^{131}	0.03	—	—	0.39

Abbreviations: LN = lymph nodes, I-^{131} = iodine, cm = centimeters, vs = versus. *p value < 0.05 is considered statistically significant.

so, for locoregional failure, the T stage and type of surgery were statistically significant (p = 0.05, 0.05, Figures 2C, 3C). T stage was the only significant factor for the distant metastases free rate (p = 0.01). No factor except the dose of RAI was significant for the overall survival (p = 0.03).

RT toxicities. Nine patients had grade 2 skin toxicity. Five patients developed grade 2 mucositis, and one had grade 3 mucositis. All patients developed grade 2 pharyngitis, 2 had grade 2 laryngitis, and 3 had grade 3 laryngitis (shown in Table 3). Two patients developed grade 2 and one grade 3 pharyngitis.

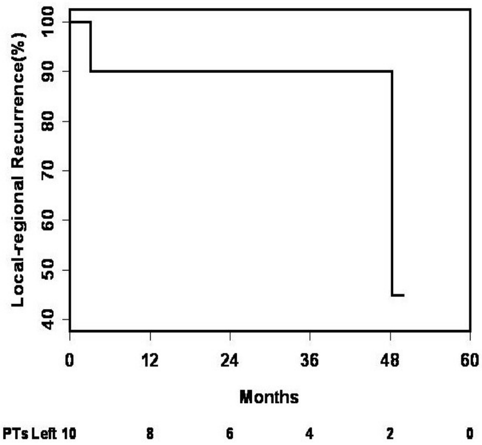
Two had grade 2 laryngitis. Four patients had grade 2 xerostomia. One patient developed respiratory distress during the course of radiation therapy and underwent tracheotomy. Also, he developed swallowing difficulty with placement of a PEG (percutaneous endoscopic gastrostomy) tube and still requires both at 3-year follow up. Another patient needed a tracheostomy tube at the time of the completion of thyroidectomy and retained the tracheotomy at the last visit (2 years and 4 months).

Table 5. Comparisons of Loco regional control rates

Authors	**Patients (n)**	**Loco regional control rate, 2 years (%)**	**Distant metastasis free rate, 2 years (%)**
Rosenbluth et al, 2005[3]	20	85%	46%
Urbano et al, 2007[4]	13	85%	NA
Our study	10	90%	87%

Abbreviations: NA= not available.

Figure 3A: Loco regional control rates for all 10 patients

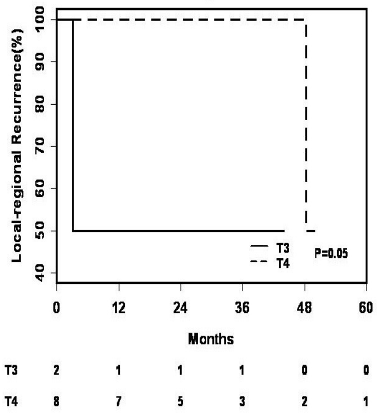


Discussion

Currently, the indications for radiation therapy in the management of thyroid cancer are controversial. The University of Florida indications[7] for PORT for differentiated thyroid cancer are in adults over 45 years of age with one of the following poor prognostic variables: positive margins, more than minimal extrathyroid extension (T4), multiple positive nodes with extracapsular extension, and disease resistant to ^{131}I.

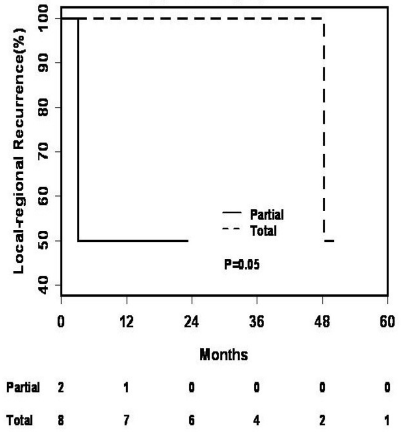
Given the complexity of treating this target volume, IMRT offers an excellent method to deliver radiotherapy adequately. IMRT for the treatment of thyroid cancer has been compared to conventional techniques in two studies.[1,5] Nutting et al[1] evaluated the potential role of IMRT in the treatment of thyroid cancer in 6 patients treated with EBRT. Conventional plans (3 fields: direct anterior and paired anterior-oblique wedge fields) were generated for each patient and compared with the 3D-CRT and IMRT plans. IMRT produced improved target coverage while reducing the volume of irradiated normal tissue ($p = 0.01$) and maximum dose to the spinal cord ($p = < 0.01$). Posner et al[5] demonstrated similar results. All the treatment plans were able to deliver a minimum dose of 60 Gy to the 95% of the gross tumor volume, while keeping the maximum spinal cord dose at or below 45 Gy.

Figure 3B: Loco regional control rates for all 10 patients based on T stage



In our series, the 3-year rates of overall survival, local control, and freedom from distant metastases were 80%, 90%, and 58%, respectively. These results are comparable with the other 2 small single institution series (Table 5). Rosenbluth[3] and Urbano[4] demonstrated locoregional control rates of 85% at 2 years. Urbano et al[4] evaluated the toxicity results of a phase I study in 13 patients treated with IMRT in locally advanced thyroid cancer. The mean PTV dose delivered to 95% of the volume was 56.4 Gy in 28 fractions (2.1 Gy per fraction, 5 fractions per week). The mean elective nodal dose was 46.4 Gy in 28 fractions (1.8 Gy per fraction). Grade 2 and 3 skin changes were seen in 31% and 38.5% of patients, while 53% and 8% developed grade 2 and 3 mucositis. No grade 4 toxicities were observed. Thirty percent of patients developed L'Hermitte's syndrome. All patients had complete responses to treatment but 3 patients developed recurrence. One had a local recurrence at 36 months, a second in the mediastinum and the lungs at 7 months, and a third had bone and lung metastases 3 months later.

Figure 3C: Loco regional control rates for all 10 patients based on type of surgery



Rosenbluth[3] et al treated 20 nonanaplastic thyroid cancer patients with IMRT. Most of their patients had T4N1 disease. The doses of RT were 54 Gy for low-risk microscopic disease, 59.4-to-63 Gy to the high risk areas, 63-to-66 Gy for positive margins, and 63-to-70 Gy to gross disease. Fourteen patients were treated with accelerated hyperfractionated RT, 1.6 Gy per fraction, twice daily. The 2-year local progression-free rate was 85%, with 2 local failures and the 2-year overall survival rate was 60%. Grade 3 acute mucositis and pharyngitis were seen in 7 and 3 patients, respectively. Only 2 patients had symptomatic grade 3 acute skin toxicity and 2 had grade 3 acute laryngeal toxicity. No significant radiation-related late effects were reported.

In the present study, the percent incidence of both and late toxicities were comparable to the reported studies in the literature. Due to the small number of patients in our series (Table 4), we could not further evaluate by multivariate analysis the influence on the outcomes of standard risk factors such as age, gender, T, N-stage, overall stage, type of surgery, margin status, number of lymph nodes positive, extra nodal extension, RAI therapy, and the addition of chemotherapy.

Conclusions

IMRT offers excellent local control rates with minimal acute side effects in the treatment of differentiated thyroid cancer in the postoperative setting. Long-term follow up is needed to assess the incidence of late toxicities. Declaration of interest: None of the authors has any financial or other potent conflict of interest. Funding: this research did not receive grants from the funding agencies.

Author Contributions

All the authors were involved in the preparation of

Table 6. Clinical characteristics and patterns of failure of 10 patients

S. No	Age year	Gender	Histology	Treatment Method	RT dose (Gy)	Type of x surgery	Status at last visit
1	52	Female	Papillary ca	SX+RAI+PORT	56	Subtotal thyroidectomy	NED
2	61	Male	Papillary ca	SX+RAI+PORT +CTX	60	Total thyroidectomy	Hilar LN and lung nodules
3	77	Male	Anaplastic ca	SX+PORT+RAI +CTX	68	Total thyroidectomy	NED
4	56	Male	Papillary ca	SX+PORT+RAI	70	Total thyroidectomy	NED
5	74	Female	Papillary ca	SX+PORT+RAI	70	Total thyroidectomy	NED
6	69	Male	Papillary ca	SX+PORT+RAI	60	Total thyroidectomy	NED
7	85	Female	Papillary ca	SX+RAI+PORT	60	Total thyroidectomy	Bone
8	69	Female	Follicular ca	SX+PORT+RAI	60	Total thyroidectomy	NED
9	77	Male	Insular ca	SX+RAI+PORT	70	Subtotal thyroidectomy	Residual disease (in-field)
10	51	Female	Papillary ca	SX+RAI+PORT	60	Total thyroidectomy	Supraclavicular LN

Abbreviations: as described in the other tables, ca = carcinoma, NED = no evidence of disease.

the manuscript. Statistical analyses were done by the biostatistician at the Fox Chase Cancer Center.

Acknowledgements. None.

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Doctor Says *No* Patient Needs to Use T3, and T3 Can Be Dangerous

In the email below, a physician wrote to a colleague of Dr. Lowe. In his email, the physician argues that *no* patient needs to use T3. He also argues that T3 can be dangerous for patients. In the right column, Dr. Lowe replies to the physician's arguments.

Subj: T3 can be dangerous
Date: Dec. 2, 2003
From: Dr. XXXXX
To: Dr. XXXXX

Dear Doctor,

I have enjoyed your emails and have read them with interest. Having done quite a bit of Thyroid [*sic*] research, and having spent three years in Dr.'s [sic] Sidney Ingbar and Louis Braverman labs, the previous and most recent authors of the medical text *The Thyroid*, I feel I can speak with a little bit of knowledge . . .

It is extremely unusual for patients not to be able to convert T4 to T3. The common exception is when patients are deathly ill and they convert T4 to rT3 (reverse T3) which is inactive; this is referred to as euthyroid sick [syndrome]. Several ICU [intensive care unit] studies have *not* shown any better survival with the addition of T3 to these patients and is not recommended.

Outpatient use of T3 with or without T4 can be dangerous. You may recall the great rematch of Mohammed Ali with Joe Frasier. Mr. Ali needed to loose [*sic*] weight to get in shape for the fight and took Thyrolar, a T4/T3 combination medicine. He lost plenty of weight and the fight early in it's course. I believe his physician also lost his job. T3 is nothing to play around with. Moreover, I am concerned with your recommendations [of T3] to the less knowledgeable.

Dr. Lowe's Reply

Tammy@drlowe.com

Our Educational/Informational Consulting Service

We provide educational/informational consulting to both patients and clinicians. Phone us at 603-391-6061, or preferably, write to us at here:

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Reply to Anti-T3 Doctor
by Dr. John C. Lowe

December 6, 2003

Dear Doctor:

A colleague of mine, to whom you wrote the email above, asked me to reply to your comments about T3. I've taken the liberty to do so because the replies to your arguments can be extremely important to the health and well-being of many patients. I hope that it's acceptable to you that I've replied.

In your email, you reach two conclusions: (1) that no patient needs to use T3 alone, and (2) that using T3 is dangerous for patients. Below, I address the implied or explicit evidence you give for these two conclusions. My point is to show that your conclusions don't validly follow from your evidence, and that your conclusions are false.

I've had decades of clinical experience with patients switching from T4 to T3. That experience compels me to respectfully but *adamantly* content that you are wrong as wrong can be about T3. Rather than T3 harming patients, for most of those who switch from T4 to T3, the T3 is tantamount to life-giving sun arising within them again—arising after years or even decades of darkness, gloom, and suffering from clinicians such as you restricting them to T4. It's T4, then, that's harmful to patients—*not T3*.

Your First False Conclusion: You first imply that no patient needs to take T3. Your reason is that except for those who are deathly ill, all patients effectively convert T4 to T3. That being the case, according to you, patients have nothing to gain by taking T3.

Many doctors mistakenly believe that patients should use T3 because they have impaired T4 to T3 conversion and, as a result, low T3 levels. But this has never been the reason for our patients using T3. Unfortunately, we're not certain why some patients must use T3 to free themselves from hypothyroid-like symptoms. Nonetheless, some patients must; T4 alone, and in some cases T4/T3 combination medicines, don't relieve their symptoms and signs; only T3 in fairly high dosages does.

One such patient was reported by Kaplan and colleagues in 1981.[1] To be healthy, the patient had to take 500 mcg of T3 per day. Testing showed that she didn't have impaired T4-to-T3 conversion, and she didn't have mutated beta-thyroid hormone receptors. Despite this, extensive testing showed that when she took this large amount of T3—and *only* then!—her metabolism was normal and she was free of symptoms. Importantly, she also had no tissue overstimulation.

We have studied and treated similar patients for the past seventeen years. We've reported our work with these patients as case reports and open systematic clinical trials,[2][3][4][5] double-blind, placebo-controlled trials,[6][7][8] and a long-term follow-up.[9] The patients' T3 dosages ranged from 50 mcg to 500 mcg—although I hasten to add that most require dosages only between 100 and 150 mcg. None of these patients had lab test results consistent with blocked T4-to-T3 conversion. Also, among those whose T3-receptor genes we sequenced, none had mutations. As with Kaplan's patient, our patients overall have remained healthy for years on these supra-physiologic dosages. None have experienced adverse health affects from their continued use of T3, and none have had evidence of tissue overstimulation upon serum and urine biochemical testing, electrocardiography, or bone densitometry. It's noteworthy that most of our patients who've recovered with T3 therapy previously failed to benefit from the use of T4 replacement.

I must comment parenthetically on one of your arguments for patients not needing to use T3. You wrote, Several ICU studies have not shown any better survival with the addition of thyroid hormone to these patients and is not recommended. This is especially true in chronic as opposed to acute renal failure.[18] We agree with you about this, based on clinical trials. The low T3 levels of most critically ill patients have a protective effect, aiding the

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patients in resting and recovering from their illnesses.

There is, however, a notable exception that the other researchers and you neglect to consider: critically ill cardiac patients who benefit from T3 treatment. Studies show that T3 improves these patients' heart function in a variety of ways. It also decreases the severity and incidence of their cardiac abnormalities, and increases their survival rate.[10][11][12][13][14][15][16] Endocrinologists might not recommend T3 for these heart patients, but some cardiologists and cardiac surgeons definitely do. Rather than doctors such as you roundly denouncing T3 therapy, you'd better serve patients' welfare by reading the relevant studies and then rectifying your judgment of T3 to reflect its safety and the potential benefits for select patients.

Your Second False Conclusion: Your second conclusion is that T3 can be dangerous. Your evidence is that Thyrolar, which contains T4 and T3, impaired Mohammed Ali's athletic performance. However, the Ali case doesn't at all logically lead to the conclusion that T3 is dangerous. I'll explain why.

Both Thyrolar and Armour Thyroid contain 38 mcg of T4 and 9 mcg of T3 per grain (60 mg). Many millions of patients have used and continue to use these products with no harm to themselves. Moreover, before the advent of the TSH test in the early 1970s, patients used these products in much higher dosages than nowadays. Yet the record does not show that patients were harmed by the higher dosages.[17] After studying 16,427 patients, Leese and Flynn recently found no increase in cardiac effects, cardiovascular disease, dysrhythmias, or fractures among patients whose TSH levels were "low." The researchers defined low as between (0.04–0.4 mU/L.[20] Most of our hypothyroid patients recover within the higher dosage range used before the early 1970s. Our meticulous safety monitoring for many years has revealed no adverse effects whatever; instead, the patients in general remain extraordinarily healthy.

However, some patients clearly do occasionally use dosages of the products that are too high for them individually. Ali was one such patient; *an excessively high dosage* left him weak, fatigued, and a poor match for Joe Frasier. The over-stimulating dosage was indeed dangerous for him—he was in the ring with Frasier, a *powerful* slugger. But Ali's over-stimulating dosage apparently didn't endanger his health in any other way. Consequently, the situational danger Ali faced certainly doesn't justify you inferring that using T3—regardless of the dosage—is dangerous in general.

Prejudice Against T3: Your conclusion that T3 is dangerous is unsound in another way. You imply that it was the T3 in the Thyrolar that impaired Ali's boxing performance. Indeed, too much T3 can impair athletic performance and can have other adverse affects. But so can too much T4. In fact, for patients whose cells effectively convert T4 to T3, too much T4 causes exactly the same adverse effects as too much T3. In that Thyrolar contains both T4 and T3, why did you attribute Ali's impaired performance only to the T3?

I suspect the answer to my question is that you hold a prejudice against T3—a prejudice you inculcated into your belief system while studying with Ingbar and Braverman. Working under the supervision of prominent conventional thyroid specialists such as Ingbar and Braverman carries a risk: The student doctor may unquestioningly accept prejudicial pronouncements by the prominent specialists—pronouncements that aren't based on research findings but instead on financial incentives from corporations. One such pronouncement is that the only thyroid hormone any patient ever needs to use is T4. Another is that T3 shouldn't be used because it's dangerous.

The student doctor, enchanted by his teachers' seeming authority, may believe the pronouncements throughout his medical career, and he may reflexly defend them without open-mindedly considering evidence that contradicts them. His reflex defense of the pronouncements may ensure that he doesn't treat patients with T4/T3 products or T3 alone. If so, he'll never learn how safe and effective these products are. He'll therefore remain miseducated about the products, and he'll lack clinical experience with them. Because of this, his conclusion that T3 is dangerous will be nothing more than a statement of prejudice that's completely without merit.

As a final note, I assume you've studied the book you mentioned, Ingbar and Braverman's *The Thyroid*. The book, which I've scrupulously studied, contains much good academic and some practical information. But the only method of thyroid hormone therapy the authors advocate and describe in the book (except in the thyroid hormone resistance chapter) is T4 replacement. So the book contains paltry little that's useful about thyroid hormone therapy. For the most comprehensive coverage of T4, T4/T3, and T3 therapies ever published, I strongly recommend my book *The Metabolic Treatment of Fibromyalgia*.[19] I suggest that you read the exhaustive information in the book on all forms of thyroid hormone therapy. Doing so is the single best way to fill the gaps and inaccuracies in your knowledge left by Ingbar and Braverman's tutelage.

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Caveat Emptor:
Different T3 Protocols

January 10, 1997

Summary: Fibromyalgia Research Foundation studies have shown that the use of T3, within the context of a metabolic rehabilitation program, can effectively improve or relieve some patients' fibromyalgia. Our studies do not provide evidence that other T3 treatment protocols are effective. Yet, some clinicians have referred to FRF studies as proof of the effectiveness of their untested T3 protocols.

"Recently, news was released that researchers at the Fibromyalgia Research Foundation (FRF) had completed blinded efficacy studies of metabolic therapy for fibromyalgia. Since then, FRF has received word from several sources that some people have perceived that our studies also vindicate various T3-based treatment protocols that have not been subjected to experimental scrutiny. I've been notified by reliable sources that several clinicians not affiliated with FRF are planning fibromyalgia treatment centers where T3 will be used to treat fibromyalgia patients. The T3-based protocols these clinicians will reportedly use are *not* the same as the one tested and endorsed by FRF researchers.

"I must emphasize that our recent blinded studies demonstrated the effectiveness of only one specific treatment protocol. I developed this protocol, through interaction with several medical colleagues, over a 10-year period. During the evolution of the protocol, we eventually abandoned all other variations of the treatment. There was one reason we abandoned the other variations: they were either comparatively or completely ineffective in the treatment of fibromyalgia. Among these abandoned protocols are the very ones some people presently perceive to be vindicated by the FRF-sponsored blinded efficacy studies.

"I encourage patients to be vigilant for several reasons. A clinician may promote T3 treatment for fibromyalgia, possibly referring to FRF-sponsored studies for evidence of efficacy, yet use a *different* protocol--one that has not been scientifically tested.

Patients should bear in mind that:

1) The treatment protocol my colleagues and I developed and clinically tested does not involve the use of T3 exclusively. About half of our fibromyalgia patients initially use T4.

2) The effective protocol involves treatment procedures in addition to the use of thyroid hormone, and for some patients, procedures other than thyroid hormone.

3) Treatment is individualized and often altered based on the patient's changing scores on five measures of fibromyalgia status and the results of physical examinations. Scores from test results are posted to five different line graphs so that changing fibromyalgia status can be visually inspected by the patient and the clinician. These objective measures and graphic displays of fibromyalgia status are *crucial* to an optimal therapeutic outcome. The physical exam assesses indirect "peripheral indices" of tissue metabolic status, such as the speed of the relaxation phase of the Achilles reflex, the resting heart rate, and voltage changes on the EKG.

4) *None* of the following are used to adjust thyroid hormone doses: basal body temperature, blood tests for serum thyroid hormone or TSH levels. For some patients, although certainly not all, the basal body temperature may be one index of metabolic change, although it is not sufficiently reliable in many patients. Regardless, if treatment is to be effective, temperature change must not be considered a goal of therapy, but rather one of several physiological indicators of a patient's response to metabolic treatment.

"I suggest that patients scrutinize information on the treatment protocol they are considering, especially if it is represented as the protocol tested by FRF researchers. This is important, because ineffective treatments are costly and disheartening to fibromyalgia patients. If fibromyalgia patients are to use metabolic therapy, I believe they should have the opportunity to undergo the treatment regimen that has been developed specifically for fibromyalgia and shown under experimental conditions to be effective for that condition. If a patient chooses to undergo an untested treatment, the clinician providing the treatment is ethically responsible for forthrightly representing it as untested--and *not* representing it, implicitly or explicitly, as the FRF protocol or a version of it."

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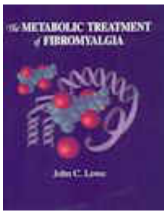

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Action Against Endocrinologists Who File Complaints Against Other Doctors for Using Treatments Other than T4-replacement

Dr. John C. Lowe

April 3, 2006

At disturbingly close intervals, a doctor or an attorney defending a doctor phones or writes to me. The story is usually the same: an endocrinologist has complained to a medical regulatory board about the doctor's practice of thyroid hormone therapy. The various complaints boil down to the same accusation: the doctor has allegedly put a patient at risk. He or she has done so by treating the patient with thyroid hormone therapy other than T4-replacement.

Occasionally a specialist other than an endocrinologist filed the complaint. Even so, one or more endocrinologists are called upon to verify the professional irresponsibility of the doctor. Medical board officials appear to consider the endocrinologists' testimony scientifically based and protective of patients. However, the endocrinologists themselves might not know it, but their testimony is just the opposite—unscientific and protective not of patients but of T4-replacement, an approach to thyroid hormone therapy that's often ineffective and harmful to patients. (It is well-documented that T4-replacement is ineffective and harmful for many patients, perhaps up to 50%. See my critiques of the T4 vs T4/T3 studies and of Dr. Richard Guttler's false and potentially harmful beliefs.)

As I document in *Tyranny of the TSH*, the endocrinologists' actions are part of a system of thuggery the purpose of which is to protect corporate profits from T4-replacement. I am not, of course, implying that any individual endocrinologist has consciously served the system in this way. As I explain in the book, some, perhaps most, of the endocrinologists are not conspiring participants; instead, I believe they are unthinking pawns in a system of greed and political tyranny.

Often, the endocrinologists' complaints are against doctors who have gotten patients well with desiccated thyroid or T3 after T4-replacement had left them suffering for years. Regulatory board members ignore this and usually cooperate by suspending or revoking the doctor's medical license. This outcome serves the system well by intimidating other doctors into restricting their patients to T4-replacement. This coercive system sustains the suffering of patients and their loved ones, consigns many patients to disability rolls, and imposes gargantuan costs on society.

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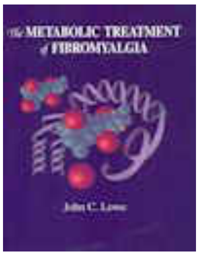

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At the root of this system is lavish funding of the endocrinology specialty and its organizations, such as the American Association of Clinical Endocrinologists, by corporations that profit from T4-replacement. The system constitutes the abuse of patients and their doctors in the service of profit and power. For humanitarian and scientific reasons, this system *must* be stopped and patients and their physicians freed from its tyranny.

In the meantime, doctors need to be protected from complaints by endocrinologists. Through our collaboration, a highly-credible, committed medical physician who is an expert in thyroid science has become active in assisting doctors who are the subject of such complaints. The assistance involves neutralizing on scientific grounds the complaints of endocrinologists. It also involves providing regulatory, legal, and financial consequences for the endocrinologists' complaints and testimony against defendant doctors.

If you are a doctor, or a patient of a doctor, against whom an endocrinologist or other specialist has filed a complaint, I encourage you or your attorney to contact me. Assertive action may block suspension or revocation of a defendant doctor's license. It may also lead to reprimand of the endocrinologist and, through civil legal action, a financial settlement from the endocrinologist. Moreover, successful action against endocrinologists will establish legal precedents in case law that will enable attorneys to halt this abusive and exploitative system. The physician/thyroid expert and I are resolutely committed to this humanitarian end.

Doctors and attorneys can reach me at drlowe@drlowe.com or 603-391-6060.

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New Self-use Device for Measuring Your Metabolic Rate: Doubts About its Usefulness

Dr. John C. Lowe

April 24, 2006

Several people have emailed us recently asking what we think of a new device that lets you measure your own metabolic rate. It is called LifeChek™. The website for the device describes it as a "direct calorimeter." That means that it uses body heat to calculate your calorie expenditure, which is another term for metabolic rate.

LifeChek™ differs from the instruments clinicians used from the late 19th century up until now to calculate a patient's metabolic rate. The instruments clinicians use calculates the metabolic rate from how much oxygen the patient consumes. But the first devices built to calculate the metabolic rate used body heat.

Lavoissier built the first one in France in the late 1700s. To calculate animals' metabolic rates, he put them in a chamber that was sealed inside another chamber. He packed the pocket between the two chambers with ice, which was available only when it snowed. The outer chamber was insulated from the outside air. The outer insulation kept room heat from melting the ice. The ice melted only from heat an animal produced inside the inner chamber. As Goran explained, "Lavoissier measured the volume of melted ice water and by so doing was able to calculate accurately the amount of heat that had to be produced by the animal to melt the measured amount of ice."[1,pp.350-1]

In the early 20th century, calorimeters that measured the heat of the whole body were in use. But they were expensive to build and operate. Also, technicians using them had trouble controlling conditions that could raise or lower a patient's body heat, so it was hard to get measurements that truly represented a patient's heat production. As a result, few of the devices were ever built and marketed. This trouble of getting measurements that actually represent whole body heat may be an even worse problem for the LifeChek™, as I'll explain below.

Dr. Gina and I are certainly in favor of people monitoring their own health with self-use devices. Thermometers, glucometers, and blood pressure kits, for example, have been a boon to millions of people. Several factors, however, determine whether a self-use device is of practical value: (1) the device must do what the manufacturer claims it does, (2) people must use the device properly, and (3) they have to interpret the test result in a meaningful way. My initial reaction to the LifeChek™ is that it's not useful in these ways. As a researcher, I can imagine some practical uses for the device, but I seriously doubt that people in general will use it in those ways. At minimum, I believe the device has serious limitations that

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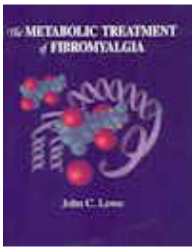

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customers should consider.

Controlling for Factors that Can Influence the Metabolic Rate. For either the heat-based or oxygen-based test to be of most practical use, the person undergoing the test must be in a resting state. Also, he or she must have properly prepared for the test. Proper preparation involves avoiding influences that can increase the amount of heat the patient generates or the oxygen he or she consumes during the test. Preparation of the person being tested, and proper conditions during the test, are absolutely essential to getting an accurate measurement.

Consider what happens when someone doesn't properly prepare for either the heat-based or oxygen-based test, or when the test isn't done under the right conditions. How much heat a person's body generates, and how much oxygen he or she consumes, can vary tremendously through the day. The variance depends on many internal and external factors. Examples are muscle contractions, emotions, processing of food, effects of stimulant chemicals, various drugs, clothing, and environmental temperature.

Measuring a person's body heat or oxygen consumption when these factors are not controlled for gives a test result that is essentially meaningless. I say meaningless because we don't know the complex of factors that have interacted to raise the person's body heat or oxygen consumption above a resting level. For example, a woman may sit down at home to use the LifeChek™ to see what her metabolic rate is at 3 PM. Is the measurement the device gives her influenced by the time of day? Is it influenced by her having just finished rearranging heavy boxes in the garage? By her sitting in a position that makes her neck muscles contract? By her keeping her ears alert for sounds of the delivery man she doesn’t want to miss? By the metabolism-driving protein lunch she had at noon? By her husband oddly not having phoned her to let her know his plane flight was safe? By the sedating wine she drank an hour before? What were the metabolism-influencing factors that influenced the measurement she got? To what extent did they interact to influence the test result? We simply can't know.

Clearly, to make sense of a metabolic rate test, we must properly prepare and properly conduct the test. In view of this, consider this statement at the LifeChek™ website:". . . LifeChek™ measures your metabolism - the calories you burn - at any given time. LifeChek™, worn discreetly, reads calories burned every 12 seconds, records the information and makes it available to you. And, you don't have to be active when measuring your calorie burn rate. You can measure when resting, watching television or even when you're eating."[2]

Dr. Gina and I follow strictly proper protocol in our clinic to ensure that we can accurately interpret the result of a patient’s metabolic test. To do so, as I said above, the patient must prepare in a particular way and go through the test under strictly controlled conditions. The LifeChek™ website indicates that you can use the device with no consideration of proper test protocol. Because of that, I have no idea how anyone could ever interpret its results meaningfully.

Variations in Skin Temperature. I have another doubt about the usefulness of the device. Judging from the pictures on the LifeChek™ website, the person straps the device onto an upper arm. The device then measures the temperature of that particular body part.

By contrast, the traditional method of calculating the metabolic rate from body heat uses a chamber akin to a full-body tanning booth. The patient lies in the chamber, and, when he or she reaches a true resting state, sensors measure the heat that the whole body emits. Someone then applies an equation that uses the patient's resting whole body heat to calculate the resting metabolic rate. In using this method, we can accurately calculate a patient’s whole-body metabolic rate only when we know for sure his or her whole-body temperature. We can use the heat of a particular body part to infer the heat of the whole body. But for the calculation of the metabolic rate to be accurate, the heat of that body part must be the same as that of the whole body. Otherwise, we'll inaccurately calculate the patient's whole-body metabolic rate.

The reason that measuring heat at only one body part may give an incorrectly calculated metabolic rate is that skin heat can vary markedly at different body sites. This is especially true of the skin of the arms. There are several reasons for this. For example, one upper arm may have more arteries coursing through it than the other. Arterial blood is warm. Because of this, the arm with the more prolific arterial tree will have a higher skin temperature than the other. As a result, the metabolic rate calculated from one arm may be different from that calculated from the other arm.

Even if the skin heat of each arm is the same, many people have troublesome body parts that can alter the temperature of the arms. Examples of such problems are muscles that are severely tense, pain-generating trigger points, thoracic outlet syndrome, and vertebral subluxations and other problems with the spine in the neck.

Noxious sensory nerve signals from these problem areas flood the spinal cord in the neck. Inside the spinal cord, the signals set off an excess of sympathetic nerve signals. These signals then pass from the spinal cord to the arteries in the skin of the arms. In response, the arteries constrict and transport less warm blood through the skin. The skin then cools. If the person uses LifeChek™ on this cooled skin, the heat it measures will be lower than the person's actual full-body heat. The device will then calculate the person's whole-body metabolic rate as lower than it actually is.

That such factors can alter skin heat in the arms leaves me with a question: Can the LifeChek™ accurately calculate the overall metabolic rate from a small skin measurement?

That many factors can interact at once to raise body heat to different levels causes me to ask another question: Without proper preparation and controlled testing conditions, will one ever know exactly what produced the heat the LifeChek™ measured?

The marketers of the device may consider my questions mere quibbles. As a metabolism researcher, however, I think the questions are important ones to ask. Nonetheless, anyone curious about the device can read about it at the following website: http://www.lifechek.com/medical.html.

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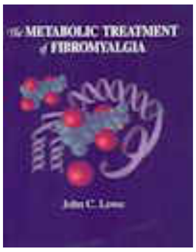

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Just to Set the Record Straight:

Educational Requirements for Admission to Medical and Chiropractic College, and for the MD Degree (Doctor of Medicine) and DC degree (Doctor of Chiropractic)

June 10, 1997

Summary: The educational requirements for the MD degree (doctor of medicine) are often exaggerated, and that of the DC degree (doctor of chiropractic) underestimated. Here, we compare the actual requirements for each degree.

A couple of years ago, I became alarmed over several posts to Internet newsgroups regarding chiropractic education. Those who wrote the posts grossly underestimated the educational requirements for the Doctor of Chiropractic degree. We spent a few days locating documents to verify the educational requirements for both MD and DC degrees. We then posted the information to the Internet. By doing so, we thought we officially set the record straight. In short order, however, I came to my senses: Presenting information that contradicts a human's well-entrenched false beliefs is not a particularly effective way to alter the beliefs. What brought me to my senses was communication with a friend, a medical physician, who read our post. As you'll see below, our post clearly shows that compared to medical colleges, chiropractic colleges require more courses for admission and more classroom hours for graduation. The documentation (see below) is a matter of public record that anyone can easily verify. Despite the facts we presented in our post, my friend/physician commented to me, "Well, yes, I see what the documentation says . . . but you know, John, MDs really do have more education." If some friends, despite learning the facts, tenaciously hold to their false beliefs about chiropractic education, I figure the public in general is even more likely to do so. Nonetheless, truths are more likely to be accepted, eventually, if broadcast persistently. So, with this in mind, I here present the documentation again--just to set the record straight. *—Dr. John C. Lowe*

Comparison of the Education of DCs and MDs

Both chiropractic and medical schools require certain course work for admission. These vary from school to school. Very few schools of either type require a bachelor's degree, although some specify that they prefer the applicant have such a degree. Chiropractic colleges do not require the MCAT. Some medical schools do. Contrary to common belief, some medical schools (including high profile institutions) require the bare minimum of undergraduate requirements. We took the admission requirements for medical schools from the publication titled: Medical School Admission Requirements, 1997-1998: United States and Canada, 47th edition (published by The Association of American Medical

Colleges). Admission requirements for accredited chiropractic schools are dictated by the Council on Chiropractic Colleges (the agency appointed by the U.S. Dept. of Education to accredit chiropractic colleges).

There has been some question on the newsgroup about the qualifications of the DC to diagnose fibromyalgia. We encourage the reader to note that chiropractic school involves between 400-to-600 more classroom hours than medical school. This was shown by two studies in the 1970s. The Parker College study more recently reported that on average, chiropractic college involves 372 more classroom hours than medical school. Chiropractic students also have more hours of training in anatomy, physiology, diagnosis, and orthopedics (the musculoskeletal system). It should be apparent from looking at the data below that in general, the chiropractic student has a more extensive classroom education and practical training in these areas, particularly in diagnosis, than the medical student.

Requirements for Admission to Chiropractic and Medical Schools

Parker College of Chiropractic

Biological Science (with lab).............1 year

General or Inorganic Chemistry
(with lab).......................................1 year

Organic Chemistry (with lab).............1 year

Physics (with lab)...........................1 year

English or Communicative Skills.........2 years

Psychology....................................1/2 year

Humanities or Social Sciences...........Not less than 15 semester hours, or 22.5 quarter hours

Electives...........From 4-to-12 semester hours, or from 6-to-18 quarter hours

Harvard Medical School

Biology (with lab)............................1 year

General or Inorganic Chemistry
(with lab).......................................1 year

Organic Chemistry (with lab).............1 year

Physics (with lab)...........................1 year

Mathematics (calculus)....................1 year

Expository Writing..........................1 year

Stanford University School of Medicine

Biology (with lab)..................................1 year

Chemistry, including organic (with lab).....2 years

Physics (with lab)..................................1 years

Johns Hopkins University School of Medicine

Biological Science (with lab).........8 semester hours

General or Inorganic Chemistry
(with lab)..................................8 semester hours

Organic Chemistry (with lab)........ 8 semester hours

Physics (with lab).......................8 semester hours

Humanities or Social Sciences.....24 semester hours

Mathematics (calculus)................4 semester hours

The following is published by the Parker College of Chiropractic, 2500 Walnut Hill, Dallas, Texas 75229 (214) 438-6932:

Degree Requirements

These basic educational requirements for graduates of both chiropractic and medical schools show that although each has its own specialties, the hours of classroom instruction are about the same. (The class hours for basic science comparisons were compiled and averaged following a review of curricula of 18 chiropractic colleges and 22 medical schools, based on the 1988-1989 Association of American Medical College Curricula.)

Minimum Required Hours
Chiropractic College/Medical College

456	Anatomy & Embryology	215
243	Physiology	174
296	Pathology	507
61	Chemistry	100
145	Microbiology	145
408	Diagnosis	113
149	Neurology	171
271	X-Ray	13
56	Psychology & Psychiatry	323
66	Obstetrics & Gynecology	284
168	Orthopedics	2
2,419	**Total Hours for Degree**	**2,047**

College Faculty

The U.S. Department of Education, through the separate accrediting agencies for chiropractic and medical schools, dictates the credentials of faculty members. In both chiropractic and medical schools, the classes for the first two academic years are usually basic sciences. Faculty members in the basic sciences divisions are either Ph.D.s in each subject taught (such as microbiology or biochemistry), or D.C.s, M.D.s, or D.O.s who also have bachelors, masters, or Ph.D. degrees in the basic science subjects being taught. Classes in the clinical sciences division are usually taught by D.C.s, M.D.s, or D.O.s. In many chiropractic colleges, M.D.s or D.O.s are permitted to teach certain courses, such as laboratory diagnosis. However, D.C.s must teach courses in which M.D.s or D.O.s don't have sufficient education or practical clinical experience.

Some chiropractic colleges have active research departments in which researchers conduct both basic science and clinical studies. The subjects of study range from biomechanics to biochemistry. Traditionally, chiropractic colleges had only minuscule research funding compared to medical schools. I recall political medicine using this fact as evidence that chiropractic wasn't legitimate. However, the medical critics failed confess that the minimal funding or lack of it was a result of political medicine doing everything in its power to block funding of studies in chiropractic college. Obviously, political medicine used a circular and disingenuous argument to deceive the public. Today, chiropractic colleges are receiving more funding for research.

Some medical schools have D.C.s as full-time faculty members. The University of Colorado School of Medicine, for example, has a full-time chiropractic radiologist as a faculty member. Dr. James P. Barassi, a chiropractor, is Research Fellow in Medicine at Harvard Medical School.

D.C.s occasionally teach part-time or special classes through medical schools. It's not unusual for D.C.s and M.D.s to co-teach both medical and chiropractic audiences. Most often, chiropractic physicians and medical neurologists or neurosurgeons co-teach.

In the late 1980s, Dr. John C. Lowe co-taught classes in myofascial pain syndromes and fibromyalgia with Robert Nash, M.S., M.D., a Virginia Beach neurologist. In 1996, Dr. Lowe also co-taught (with Baylor University College of Medicine faculty member Richard Garrison, M.D.) a continuing education class for M.D.s on myofascial pain syndromes. This class was presented through the post-graduate education department of the family medicine department of Baylor University College of Medicine. On another occasion, Dr. Lowe and Dr. Garrison co-presented grand rounds in the Baylor family medicine department. The presentation was about Dr. Lowe’s hypometabolism hypothesis and his treatment protocol. A research nurse who recovered from fibromyalgia with our metabolic treatment protocol (administered by a family medicine resident under the supervision of Dr. Garrison) attended for questioning from medical students, faculty, and residents. Dr. Lowe has also lectured on his studies of fibromyalgia to the research staff at the Department of Family Practice and Community Medicine, University of Texas, Houston Health Science Center in Houston, TX. Such cooperative interactive teaching between chiropractic and medical physicians is become progressively more common.

Licensing and Postgraduate Education

The chiropractic physician must pass three levels of national board exams and a physical therapy exam to be eligible to sit for state board examinations. State board exams involve both written examination and oral practical exams involving clinical practice and x-ray interpretation.

After graduation, the DC may undergo postgraduate training to become board certified as a chiropractic radiologist, neurologist, orthopedist, internist, family practitioner, sports physician, rehabilitation specialists, clinical nutritionist, or pain management specialist. Medical physicians also may become board certified. Options such as surgery are open to medical and osteopathic physicians. Board certification is not necessary for either type of physician to become licensed and to practice. Chiropractic physicians are required to obtain continuing education units each year for license renewal.

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"If the new paradigm for the healing arts is going to serve us better than the old one—"

Comments by Dr. John C. Lowe as a participant at the First Congress on Defining a New Paradigm for the Healing Arts

University of Texas, Health Science Center
Houston, Texas, May 28-31, 1998

On May 13, 1998 (during the pre-Congress Internet communications of participants), John Diamond, M.D. made several comments I wholeheartedly agree with. I concur with him (at the risk of misrepresenting what he wrote) on several points: Modern medicine was destined to fail in its presumed attempt to provide the public with health and well-being when it: (1) subscribed to the Cartesian division between mind and body; (2) assumed symptoms to be "errors by the body," the removal of which constitutes a "cure"; and (3) ignores biological individuality.

In concluding, he made another statement I agree with: "One of the great pitfalls of emerging paradigms is to use the old paradigm's benchmarks to justify, prove, or define itself." Implying that the scientific method was a benchmark of the paradigm that is presently crumbling, his next statement was ". . . the scientific method may be inappropriate." This statement raises in my mind the issue of what I view as a fundamental fault in the old paradigm. It is a fault that, if not corrected, threatens to compromise the value of the new paradigm. The fault is a failure to use the scientific method, by which I mean the rigorous use of correct reasoning in the formation of our scientific beliefs. I believe the three conceptual faults of the old paradigm that Dr. John Diamond mentioned are a product of this underlying problem. (Incidentally, many people seem struck with disbelief when I remark that the scientific method has been sparsely and poorly applied in medical science. Nonetheless, some argue (see the two references below[1][2]) that despite the massive amount of published research, the effectiveness of only about 15% of medical interventions has been validated by formal scientific methodology.)

My old friend, Robert S. Mendelsohn, M.D. (who, if still alive, would have enthusiastically taken part in this Congress), made this point back in the 1980s in several books (*Confessions of a Medical Heretic*, *MalePractice: How Doctors Manipulate Women*, and *How to Raise a Health Child in Spite of Your Doctor*). Bob argued that what the popular press calls medical science is more accurately described as the Church of Modern Medicine. In his analogy, physicians are the priests, and their aim is to persuade the congregation of patients to submit to the authoritarian dogma of the Church. His point was well taken: He catalyzed a movement of patients and heretical physicians who defiantly challenged the dogma.

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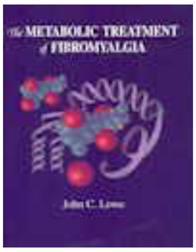

The Metabolic

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This movement contributed to the current widespread determined opposition to orthodox medical authority.

Despite this opposition, I suspect that most people will continue to acquiesce to authoritarian medical dogma. They find it easier to accept without question the axioms, postulates, and other assumptions issued by others, and then let the chips fall as they may. This tendency is not all bad, of course. The volume of new information that flows forth necessitates that we often trust the judgments of those we consider authorities. But problems can develop when we take careless advantage of this convenience. Thus, for illustration, it appears that incalculable numbers of people have died of heart disease that could have been averted, had they taken enough supplemental B vitamins and lowered their homocysteine levels. But they failed to do so. Why? Their well-meaning but misguided physicians assured them that medical science had proven that we get enough vitamins in our foods and that vitamin supplements are of no value.

As another illustration, a medical researcher may ignore important clues to the solution to medical problems, delaying the solution for decades. The reason? Because he compliantly accepts as scientifically established a dogmatic belief of authorities in a field that overlaps his own--a belief falsely professing that a particular class of clues is irrelevant to the problem he is studying. Let me give a brief example of this. Richard Garrison, M.D., others, and I are actively studying the use of thyroid hormone as a treatment for fibromyalgia. More times than I can count, my particular efforts with this experimental treatment have been seriously hampered by authoritarian dogma accepted as scientific fact. The problem is the current clinical paradigm of endocrinology. This paradigm is expressed in a false proposition: that the serum basal TSH level is the "gold standard" for diagnosing thyroid hormone deficiency and for adjusting the patient's dosage of thyroid hormone. In line with this, those who believe this proposition make two pronouncements: (1) If the TSH level is within the normal range, then the patient cannot possibly have too little thyroid hormone regulation of cell function, and (2) taking enough thyroid hormone to suppress the TSH level is hazardous and possibly life-threatening. Based on these false beliefs, many physicians have actively opposed my use of our treatment that ignores these mandates yet gets patients well.

Acceptance of authoritative dogma is synonymous with a rejection of the first rule of reason of traditional rationalism. This rule says to examine the relevant evidence before accepting and acting on a belief. It is this that I believe is the more fundamental fault underlying those that Dr. John Diamond listed. It is also the reason philosophers of science generally consider medical science primitive and unsophisticated. I believe a novel solution would be a commitment by medical clinicians and researchers to a purely rational path to our beliefs. I believe we should: (1) question all preconceived ideas; (2) refuse to unquestioningly accept anyone's belief, except for temporary expedience, simply because he or she is considered an authority; (3) willingly, albeit cautiously, abandon beliefs that conflict with the available evidence; and (4) tentatively adopt rather than dogmatically adhere to beliefs that are best supported. It seems to me that this approach is one we must adopt, if the emerging new paradigm for the healing arts stands a chance of serving us better than the old one.

References

[1] Smith, R.: Where is the wisdom? The poverty of medical evidence. *British Medical Journal*, 303:798-799, 1991.

[2] Rachlis, N. and Kuschner, C.: *Second Opinion: What's Wrong with Canada's Health Care System and How to Fix It*. Toronto, Collins, 1989.

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"Only T4 is Transported into the Brain": A Widespread False Belief

Dr. John C. Lowe

April 24, 2006

Not a month passes that someone, a doctor or a patient, writes or says to me, "T3 can't pass the blood-brain barrier into the brain." These people include this phrase in a variety of contexts. Some ask questions, others make assertions, and some criticize a statement of mine that's relevant to this belief. But each communication is undergirded by the presumption that the belief is true.

To illustrate, two days ago, a patient emailed this typical statement to me: "I've been doing more reading on the Internet. An article I came across talked about T3 not being able to cross the blood-brain barrier, and for that reason, it's good to take some T4 as well as T3."

Some patients and physicians include the presumption in thoughtful discourse. For example, two weeks ago, a physician wrote and asked essentially: "Since T3 does not cross the blood-brain barrier, then the T3 a patient takes orally cannot influence the pituitary gland's secretion of TSH. But this doesn't reconcile with my clinical experience. I've seen scores of patients' TSH levels decrease in response to oral T3 medication. I guess thyroid physiology is just very complex."

Let me say right up front, *resoundingly*, that this belief is false! It is an institutionalized falsehood that tenaciously thrives in the minds of both patients and physicians. It reminds me of gossip I used to hear as a young man in small backwood towns of South Alabama and Northwest Florida. Someone would say, "Word is, ol' Mathews been cheatin' people round town. Must be so, 'cause they don't let him pay with checks at the grocery store anymore." I was amazed at how stubbornly these people held to their allegations, despite evidence that they were ill-founded. If they stood in line behind ol' Mathews at the grocery checkout counter and watched him pay with a check, they would later tell others how stupid the clerk was for forgetting to reject the check from the ol' cheat. Then, undaunted, they would go right on gossiping about ol' Mathews.

I earnestly hope that patients and physicians are more corrigible than those good ol' country folks were. We *must* dispel this false belief because it can influence decisions about patients' thyroid hormone therapy. I've had patients through the years who had fully recovered using T3 alone with no adverse effects whatever, only to become ill again when a well-intended doctor reduced the patient's T3 dose and added some T4—just to make sure the patient's brain wasn't deprived of thyroid hormone.

Five years ago, on the same day, I received letters about this belief from a medical doctor and chiropractic doctor, both of whom practiced in

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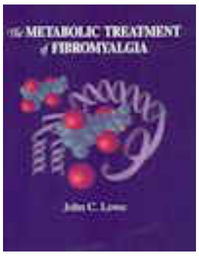

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France. As I read their letters in close tandem, it brought to mind the trail of similar letters to me that spanned back, at the time, some twelve years. I reacted by researching and writing an article in which I showed that the belief is false. At the time, I was deluged with other responsibilities, and so I didn't post the article to drlowe.com or submit it elsewhere for publication. Each time I received another letter or email from a patient or physician, I thought again about publishing the article.

Finally, on August 17, 2005, we published the article on drlowe.com. Before doing so, I revised it to include a new discovery about T3 and the brain. Since I've continued to receive correspondence in which authors reiterate the false belief, I decided to write this piece to bring attention again to the 2005 article.

This false belief is virtually an indelible stain in the memory of patients and physicians, and to clear it away, I think we'll have to scrub long and loud with the solvent of truth. The new electronic journal *Thyroid Science* (www.thyroidscience.com), a publication for patients, clinicians, and researchers, will become active later this year. When it does, we must publish a review paper documenting that T3 does indeed enter the brain. And we must keep the paper prominently display for the world to see.

For those who don't want to read the 2005 article, I'll summarize here what I documented in the article: "Transthyretin" is the protein that transports T4 across the blood-brain barrier. It also transports T3 across. It may transport less, however, because the binding affinity of the receptors within the protein is about ten times less for T3 than for T4. Nonetheless, this protein does indeed transport T3 and T2 into the brain across the blood-brain barrier. However, T3 also enters the brain, at least in mice, without riding in on transthyretin.

Transthyretin also transports chemical contaminants such as dioxins and PCBs across the barrier. The latter chemicals displace T4 and T3 from the thyroid hormone receptors inside the transthyretin molecule. Since all humans are polluted with these contaminants (this is what toxicologists tell me), the displacement of T4 and T3 may be a major mechanism of health problems from a brain deficiency of thyroid hormone. The potential health problems from this displacement are highly complex. In *The Metabolic Treatment of Fibromyalgia*, I wrote an extensive section on the topic. In the section, I noted that after contaminants displace T4 and T3 from transthyretin, bind to the hormone receptors in the protein, and then ride the protein into the brain, the contaminants can bind to thyroid hormone receptors on genes. The binding alters the normal transcription activities of the genes, producing adverse effects that are hard to predict and diagnose.

To sum up, the belief that T3 doesn't cross the blood-brain barrier is false. The documentation is far from new. It is high time, then, that we pluck this false belief out of patients' and doctors' frames of reference and dispose of it once and for all.

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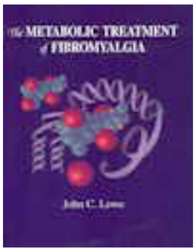

A Response to Robert Loblay, M.D.

June 10, 1997

Summary: Here, Dr. Lowe responds to an Internet post by Robert Loblay, MD. In his post, Dr. Loblay advised fibromyalgia patients with normal thyroid function *not* to use thyroid hormone unless they have thyroid cancer or multinodular goitre.

An OzME subscriber in Australia sent the following post written by a physician. She asked if I would comment on his statements. I did so because in his post, he expressed a view that I steadfastly disagree with, and because he questioned the ethics of my colleagues and me.

He wrote: "I don't normally consider it appropriate to enter into discussions about various treatments people are trying out. However, I feel it is important to warn you of potential dangers. I'm not aware of any solid evidence that FMS is a "hypometabolic" condition, and would not advise anyone whose thyroid function is normal ("euthyroid") to take thyroid hormones (T3 - tertroxine; T4 - oroxine) unless they have thyroid cancer or multinodular goitre.

"At doses of around 200 mcg or above thyroid hormones are likely to cause loss of calcium through the urine, with a long-term risk of osteoporosis. At doses of 300-400 mcg and above there is a risk of developing clinical features of thyrotoxicosis. These include damage to the skeletal and heart muscles. Long-term overuse could lead to muscle wasting, weakness and heart failure.

"To find out whether your thyroid function is normal, ask your doctor to do a blood test to check your TSH level (Thyroid Stimulating Hormone). Melatonin is not likely to cause any long-term harm as far as anyone knows at present. However, I think people should be very circumspect about following the advice of a doctor who prescribes thyroid hormones in these circumstances. Many professionals would regard it as bordering on malpractice."

Dr. Robert H. Loblay
Immunology Unit
Department of Medicine, D06
University of Sydney, NSW 2006

Dr. John C. Lowe' Response:

Dear Dr. Loblay:

I appreciate your apparent motive of informing OzME subscribers of what you consider possible dangers of thyroid hormone therapy. Well-intended as I assume your statements were, they are misguided and inappropriate, and I must take issue with several points you raised.

You wrote that you are not aware of any solid evidence that FMS is a "hypometabolic" condition. There is ample evidence for this, although there is no accounting for your not being aware of it. I would hope that your inquiries into the nature of various health care conditions would extend beyond the major indexing systems, such as Medline. As a medical editor, I am lamentably aware of the inadequacies of the indexing systems in distributing scientifically-based information to researchers and clinicians across the globe. Some 80% of all biomedical publications are not indexed in Medline. In addition, most indexing systems publish abstracts of only a limited number of publications. My point is that the entire mass of biomedical information is available to literally no one. Only those claiming omniscience would express surprise at learning of a view he or she had never heard before. The inadequacies of the dissemination of biomedical information seem so obvious to me that I am always puzzled when I hear someone express surprise or disbelief at new information. To bring yourself up to steam on the subject, you might read our article on euthyroid fibromyalgia in the February, 1997 issue of *Medical Hypotheses* (this one *is* in Medline). For the purposes of responding here to your comments, however, I will say that the only comprehensively plausible hypothesis of fibromyalgia at this time is that the features of the condition are a product of inadequate thyroid hormone regulation of gene transcription, whether due to hypothyroidism or cellular resistance to thyroid hormone.

You wrote that you would not advise anyone whose thyroid function is normal ("euthyroid") to take thyroid hormone unless he or she has thyroid cancer or multinodular goitre. Perhaps you are not aware of the phenomenon of cellular resistance to thyroid hormone of euthyroid individuals (those with normal thyroid function test results). One cause of resistance to thyroid hormone is mutant T3 receptors that have a low affinity for the hormone. Studies using molecular biology techniques have shown why most of these patients, who have hypothyroid-like symptoms, recover only when they use relatively large (supraphysiologic) dosages of T3. In some of our research patients, dosages have ranged from 75 mcg of T3 to as much as 300 mcg. The highest dosages on record necessary to free resistance patients from their symptoms is 500 mcg of T3 and 1000 mcg of T4. Yet, these dosages do not cause tissue thyrotoxicosis in these patients.

We have conducted 5 studies with euthyroid fibromyalgia patients (3 were blinded studies) over the past several years. We have done extensive testing with bone densitometry, serial ECGs, and serum and urine tests to detect toxicity of heart, bone, liver, and muscle. But we have found no adverse tissue effects. What we have clearly demonstrated in these studies is that euthyroid fibromyalgia patients have peripheral cellular resistance to thyroid hormone. We do not know the cause of the resistance yet, but it is certain at this time that these patients have cellular resistance to thyroid hormone. We are in the planning stages now of setting up a genetics and molecular biology laboratory to try to identify the mechanism of the resistance. I wonder, would you deny these patients thyroid hormone, in line with your advice to OzME subscribers, because they are euthyroid and do not have thyroid cancer or multinodular goitre?

With the treatment protocol we use, our hypothyroid fibromyalgia patients typically recover even more readily than our euthyroid fibromyalgia patients. What we do to alleviate the fibromyalgia symptoms and signs of these patients is merely raise their dosage of T4 into the range that you warned patients not to take--200 to 400 mcg (0.2 to 0.4 mg). Contrary to your warning, however, extensive testing has shown that these dosages cause no tissue thyrotoxicity in our hypothyroid patients, just as with our euthyroid patients on T3. In both the euthyroid and hypothyroid patients, the serum TSH levels are suppressed, but I emphasize, with no adverse tissue effects whatsoever.

I bring this up because of your warning that dosages over 200 mcg (0.2 mg) are likely to cause adverse effects. You listed "loss of calcium through the urine, with a long-term risk of osteoporosis." You also wrote: "At doses of 300-400 mcg and above there is a risk of developing clinical features of thyrotoxicosis. These include damage to the skeletal and heart muscles. Long-term overuse could lead to muscle wasting, weakness and heart failure." It is true that some patients' tissues may be overstimulated at these dosages. Because of this, we evaluate each patient as an individual to assure his or her safety. Nevertheless, your statements are highly misleading and are not supported by the scientific literature.

First, the argument that dosages of thyroid hormone that suppress the TSH level (usually dosages over 200 mcg) cause loss of calcium in the urine simply is not true in general. There may be a slight increase in bone turnover. This is indicated in some of our patients by an increase in the urine levels of hydroxyproline or N-telopeptides. But seldom do T4 dosages as high as 300-400 mcg cause an increase in serum or urine calcium, phosphorus, alkaline phosphatase, or creatine. What's more, studies during this decade have shown that the increase in bone turnover (indicated by increases in hydroxyproline or N-telopeptides) is *not* associated with a decrease in bone density, and certainly not with the development of osteoporosis that you propose. The increase in bone turnover occurs during the first year a patient begins taking thyroid hormone, but then the turnover ceases. In the 1980s, some researchers tested patients only during the first year after they had started using T4. They found increased bone turnover and argued fallaciously that this portended osteoporosis and an increased rate of fractures. When other researchers tested patients between 1 and 2 years after starting T4, they found that the bone turnover had subsided. What this suggests is that hypometabolic tissues such as bone initially have a hypersensitivity to thyroid hormone, but that the hypersensitivity is transient and normalizes after a year or so. We have conducted follow-up testing of fibromyalgia patients who have used thyroid hormone for 1-to-5 years. In general, our patients have bone density *above* that for age- and sex-matched controls. Other researchers have reported the same finding in non-fibromyalgic patients. Some patients taking higher-end dosages have had higher bone density. The increase in bone density is probably a result of the increase in physical activity of the patients after the thyroid hormone medication metabolically capacitates them. (I should note, however, that postmenopausal women who do not take estrogen are at risk for loss of bone density. It is *not established*, however, that this leads to osteoporosis or progression of bone loss into the fracture risk range.)

You also mentioned muscle wasting as a result of the prolonged use of relatively high dosages of thyroid hormone. We have not found an increase in serum or urine creatine in our patients on high thyroid hormone dosages. This rules out breakdown of lean tissue mass. Patients do lose a small amount of weight, but this results from a slight degree of fat depletion associated with their increased activity levels. Certainly, it is not muscle wasting.

You also warned of adverse cardiac effects. We have performed hundreds of ECGs on hypothyroid and euthyroid fibromyalgia patients both before and during thyroid hormone therapy. Before treatment, the ECGs of many hypothyroid and euthyroid patients indicate a "hypothyroid heart." These results include low voltage deflections in the QRS complex, flattened or shallow inversion of T waves in all or most leads without comparable ST displacement, prolonged QT intervals, and sinus bradycardia. These ECG phenomena in our patients are corrected with thyroid hormone therapy. We have also found that treatment with the range of dosages you warn against has produced in our patients none of the classic "thyrotoxic heart effects" such as shortened QT interval, prolonged or shortened PR interval, ST segment elevation, U waves, or Wolfe-Parkinson-White syndrome.

The genesis of the misguided concerns you expressed was a number of studies published in the early 1970s. Researchers tested patients taking 200-400 mcg of T4--common therapeutic dosages at the time, but dosages that suppressed the TSH level. They found "abnormal" values for a number of biochemical measures, and changes such as increased heart rate during sleep. There was no evidence that these findings were harmful to the patients, but the researchers *speculated* that the findings would eventually lead to significant health problems. They advised clinicians not to permit patients to take more than 100 to 200 mcg--the amount that keeps the TSH within the normal range. Clinicians complied, and as a result, we read statements by clinicians such as yourself, advising patients to get their TSH levels checked. (You wrote, "To find out whether your thyroid function is normal, ask your doctor to do a blood test to check your TSH level.") The well-intended but scientifically unjustified conclusion that the only safe and effective T4 dosage is one that keeps the TSH within the normal range started in 1973. Since then, complaints by patients that these dosages leave them symptomatic have become legend. It is a sad commentary on modern medical practice that clinicians now strive for a mid-range TSH and ignore the fact that it leaves many patients suffering--all because of a speculation made almost 25 years ago that has failed to be supported by subsequent scientific studies. I want to emphasize for you: studies have *not* confirmed the conjecture that dosages of 200-400 mcg cause patients any harm. Quite to the contrary, some studies have shown that these dosages are the only ones that benefit many patients. Still, though, most patients are denied the opportunity to determine whether such dosages are beneficial for them. The reason is that this speculation has now become entrenched in the unquestioning minds of many clinicians. As a result, hypothyroid patients the world over, including hypothyroid fibromyalgia patients, live a life of hell because of what I call the tyranny of the TSH.

Certainly, each patient must be considered on an individual basis, which we do at the Fibromyalgia Research Foundation. But in general, the scientific evidence does not support the conjecture that patients taking 200-400 mcg of thyroid hormone will be harmed by these amounts. I only wish that physicians had the same concern for the potentially harmful effects of patients not being treated with thyroid hormone when it is needed, or with denying them a high enough dosage. These possible effects include elevated cholesterol and triglycerides, hypertension, enlarged heart, ischemic heart disease, vacuolated degeneration and fibrosis of the heart, congestive heart failure, primary biliary cirrhosis, learning disabilities, cognitive impairment, and suicidal depression. As Bastenie has written, having too little thyroid hormone is a destructive process.

You wrote in conclusion, "I think people should be very circumspect about following the advice of a doctor who prescribes thyroid hormones in these circumstances. Many professionals would regard it as bordering on malpractice." I can excuse your ignorance of medical history and the science of thyroidology. But I take offense at the last statement, which constitutes an authoritarian attempt at intimidation. I am a research scientist and logician. As such, I pride myself on basing my opinions and conclusions on credible evidence. I am fully prepared to defend with evidence from the scientific literature and the studies of my own research team, each and every statement I make. On the other hand, your statements are the mere parroting of the false conclusions of others. If you consider yourself scientifically oriented, then you have a responsibility to examine the evidence relevant to an issue you give advice on. You have a responsibility to make your advice conform to what the scientific evidence indicates. Otherwise, you violate ethical standards of scientific conduct, and in that case, it is you who may be guilty of a form of malpractice. Fibromyalgia patients have suffered enough from misinformation. Out of compassion for them, you should consider this before disseminating further scientifically invalid information to them. I suggest that you go to the primary sources, and with an open mind, infer for yourself exactly and only what the evidence dictates. Should you do this, I am confident that you will rectify the well-intended but misguided warning you posted to the OzME subscribers.

---Dr. John C. Lowe

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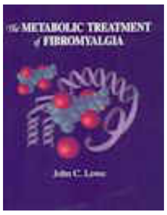

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T3 & Physiological Instability

July 27, 2000

On June 11, 2000, I replied to a question from a physician about a presumed problem with patients taking plain T3. We've posted the question and answer here because over the past six months, I've received many e-mails asking the same question the physician asked. The e-mails appear to be prompted by a physician advising patients on the Internet that plain T3 causes "physiologically inconsistent responses." As a remedy for this supposed problem, the physician recommends one of two solutions: (1) take timed-release T3 instead of plain T3, or (2) take plain T3 after eating. I don't believe there is any point to these supposed "solutions." First, taking T3 after eating interferes with its absorption from the GI tract. One could get the same effect by reducing the amount taken on an empty stomach. But even that supposed solution is pointless in that it addresses a problem that doesn't exist. I say this because I don't believe plain T3 causes clinically relevant inconsistent physiological responses. I explain below in my reply to the physician.

Dear Dr. Lowe: I am a physician practicing nutritional, holistic, and preventive medicine. I have a question related to your recommending the use of Cytomel instead of compounded timed-release T3. I've been using timed-release T3 for about a year, and I feel my results have been pretty good. Some of my patients have recently requested that I treat them according to your protocol. They want me to switch from the timed-release T3 to plain T3. My understanding is that plain T3 has such a short half life in the body. And because of that, it's hard to get consistent physiologic responses unless patients take the hormone several times per day. My understanding is that even then, results are variable. Please advise me of your experience with this. Thank you.

Dear Doctor: For many years, I've heard physicians express a precaution that plain T3 causes inconsistent physiologic responses. In particular, I've heard that plain T3 causes cardiac arrhythmias. I've long had a particular interest in these precautions. After hearing the precautions, I began meticulously comparing the effects on patients of different thyroid hormone preparations. I've compared the effects, on the one hand, by careful clinical observations. I've also done so, however, by extremely systematic monitoring of patients, including serial EKGS and, when needed, cardiac consultations. From these comparisons, I can say emphatically that among my patients, I've seen no evidence of inconsistent physiologic responses to plain T3.

I've found that some patients have markedly improved or recovered with the use of timed-release T3. I assume that most of these patients were hypothyroid. However, I've also found that many patients either don't benefit with timed-released T3, or they improve only slightly. When we switch these patients to plain T3, most have markedly improved or completely recovered. (Of course, the use of thyroid hormone isn't the only component of our patients' regimen. We require that all patients engage in a more comprehensive regimen of metabolic rehab. So, when I refer to a patient improving under our care, invariably, the patient has also engaged in other metabolism-regulation methods. Such methods include diet modifications, nutritional supplementation, and exercise to tolerance.)

I suspect that the reason most patients don't have inconsistent physiological responses to pain T3 is a "buffering effect" of the "genomic" actions of T3. Most effects of T3 on the body are not a result of direct actions of the hormone on cells. Instead, most effects of T3 result from the actions of the hormone on genes in cell nuclei. These genomic actions of T3 appear to serve as a "buffer." By this I mean that most cells are protected from a direct, abrupt effect of T3. The physiologic effects of T3 are highly *indirect*. The effects result from changes in protein synthesis due to T3-induced alterations in gene transcription.

When a patient takes T3, the hormone must first enter the cells and then enter their nuclei. Next, the hormone must bind to T3-receptors on different genes. The binding of T3 to T3-receptors on genes alters the genes' transcriptional activity. Transcription of some genes is activated; that of others is inhibited. The resulting increase in messenger RNA from the activation of genes may also be enhanced by post-transcriptional actions of T3. For example, T3 may increase the survival time of some messenger RNAs. The increase or decrease in gene transcription (resulting from the transcription-regulating effects of T3/T3-receptor binding on genes) changes the numbers of proteins synthesized by cells. The change in concentrations of the proteins then alters physiology. For instance, the concentration of the apoenzyme component of various enzymes is increased. The increase in the concentration of the enzymes then alters the rate of different biochemical reactions, and this is reflected in changed physiology.

Some patients report that they perceive rapid effects after consuming plain T3. If these effects are real, it's unlikely that they are induced through the genomic route. Some genomic effects of T3 in isolated laboratory media may occur within minutes after cell nuclei are exposed to T3. But this observation doesn't translate into physiological and clinical effects in humans taking T3 by mouth. Most physiologic and clinical effects of swallowed T3 have much longer latencies—some effects may take days, weeks, or even months.

There are a few known exceptions to this rule of "genomic buffering." Most functions of heart and liver cells, like those of other tissue cells, are altered by T3 acting through heart cell genes. But the heart and liver respond in some ways directly to T3. Presumably, this rapid effect occurs following T3 binding to T3-receptors outside cell nuclei, such as on the plasma membrane. As a result, some patients may experience a mild increase in heart rate or force of contraction within a couple of hours after taking their single daily dose of plain T3. Fibromyalgia patients may be especially perceptive of these transient changes in heart function because of a generally heightened sensitivity to body sensations. In my experience, however, this quick response of the heart to T3 is clinically irrelevant except in one group of patients—those with severely compromised cardiac function or underlying cardiac abnormalities. (I hastily add that while we must take great care to ensure the safety of such patients, the judicious use of T3 may be critical to some of these patients improving their cardiovascular status. As I described on pages 885 and 886 of T*he Metabolic Treatment of Fibromyalgia*, T3 is being used as a form of treatment for patients with some cardiac abnormalities.)

Rarely, a patient reports that she has a detectable response to plain T3 *within minutes* after ingesting it. My impression is that most of these patients expect T3 to produce an almost instantaneous effect. I say this because of my questioning of these patients. I find that most don't understand that time-consuming genomic actions mediate the majority of the physiological effects of T3. It's possible, of course, that some patients have a rapid allergic reaction to some non-hormonal component of the tablets that contain T3. Also, perhaps a few patients experience some nebulous "energy" effect after ingesting T3 but before absorbing it. Other than these possible exceptions, no physiological effects from T3 should occur until after the T3 passes from the GI tract into the blood. As I explained in Chapter 5.4 of *The Metabolic Treatment of Fibromyalgia*, circulating blood levels of T3 reach a peak 2-to-4 hours after a patient ingests it. Absorption is not immediate. After absorption, some non-genomic effects may occur after an hour or two. As I said, though, my observations and objective testing compel me to reach two conclusions: (1) that few if any patients have "inconsistent physiological responses" other than a mild increase in heart rate or force of contraction, and (2) except for the rare patient, these cardiac effects are clinically unimportant.

I hope my answers are of some value to you.

Best regards,
Dr. John C. Lowe

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"Only T4 is Transported into the Brain": A Widespread False Belief

Dr. John C. Lowe

April 24, 2006

Not a month passes that someone, a doctor or a patient, writes or says to me, "T3 can't pass the blood-brain barrier into the brain." These people include this phrase in a variety of contexts. Some ask questions, others make assertions, and some criticize a statement of mine that's relevant to this belief. But each communication is undergirded by the presumption that the belief is true.

To illustrate, two days ago, a patient emailed this typical statement to me: "I've been doing more reading on the Internet. An article I came across talked about T3 not being able to cross the blood-brain barrier, and for that reason, it's good to take some T4 as well as T3."

Some patients and physicians include the presumption in thoughtful discourse. For example, two weeks ago, a physician wrote and asked essentially: "Since T3 does not cross the blood-brain barrier, then the T3 a patient takes orally cannot influence the pituitary gland's secretion of TSH. But this doesn't reconcile with my clinical experience. I've seen scores of patients' TSH levels decrease in response to oral T3 medication. I guess thyroid physiology is just very complex."

Let me say right up front, *resoundingly*, that this belief is false! It is an institutionalized falsehood that tenaciously thrives in the minds of both patients and physicians. It reminds me of gossip I used to hear as a young man in small backwood towns of South Alabama and Northwest Florida. Someone would say, "Word is, ol' Mathews been cheatin' people round town. Must be so, 'cause they don't let him pay with checks at the grocery store anymore." I was amazed at how stubbornly these people held to their allegations, despite evidence that they were ill-founded. If they stood in line behind ol' Mathews at the grocery checkout counter and watched him pay with a check, they would later tell others how stupid the clerk was for forgetting to reject the check from the ol' cheat. Then, undaunted, they would go right on gossiping about ol' Mathews.

I earnestly hope that patients and physicians are more corrigible than those good ol' country folks were. We *must* dispel this false belief because it can influence decisions about patients' thyroid hormone therapy. I've had patients through the years who had fully recovered using T3 alone with no adverse effects whatever, only to become ill again when a well-intended doctor reduced the patient's T3 dose and added some T4—just to make sure the patient's brain wasn't deprived of thyroid hormone.

Five years ago, on the same day, I received letters about this belief from a medical doctor and chiropractic doctor, both of whom practiced in

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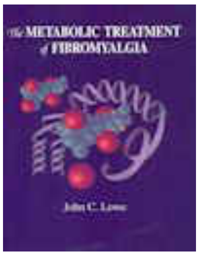

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France. As I read their letters in close tandem, it brought to mind the trail of similar letters to me that spanned back, at the time, some twelve years. I reacted by researching and writing an article in which I showed that the belief is false. At the time, I was deluged with other responsibilities, and so I didn't post the article to drlowe.com or submit it elsewhere for publication. Each time I received another letter or email from a patient or physician, I thought again about publishing the article.

Finally, on August 17, 2005, we published the article on drlowe.com. Before doing so, I revised it to include a new discovery about T3 and the brain. Since I've continued to receive correspondence in which authors reiterate the false belief, I decided to write this piece to bring attention again to the 2005 article.

This false belief is virtually an indelible stain in the memory of patients and physicians, and to clear it away, I think we'll have to scrub long and loud with the solvent of truth. The new electronic journal *Thyroid Science* (www.thyroidscience.com), a publication for patients, clinicians, and researchers, will become active later this year. When it does, we must publish a review paper documenting that T3 does indeed enter the brain. And we must keep the paper prominently display for the world to see.

For those who don't want to read the 2005 article, I'll summarize here what I documented in the article: "Transthyretin" is the protein that transports T4 across the blood-brain barrier. It also transports T3 across. It may transport less, however, because the binding affinity of the receptors within the protein is about ten times less for T3 than for T4. Nonetheless, this protein does indeed transport T3 and T2 into the brain across the blood-brain barrier. However, T3 also enters the brain, at least in mice, without riding in on transthyretin.

Transthyretin also transports chemical contaminants such as dioxins and PCBs across the barrier. The latter chemicals displace T4 and T3 from the thyroid hormone receptors inside the transthyretin molecule. Since all humans are polluted with these contaminants (this is what toxicologists tell me), the displacement of T4 and T3 may be a major mechanism of health problems from a brain deficiency of thyroid hormone. The potential health problems from this displacement are highly complex. In *The Metabolic Treatment of Fibromyalgia*, I wrote an extensive section on the topic. In the section, I noted that after contaminants displace T4 and T3 from transthyretin, bind to the hormone receptors in the protein, and then ride the protein into the brain, the contaminants can bind to thyroid hormone receptors on genes. The binding alters the normal transcription activities of the genes, producing adverse effects that are hard to predict and diagnose.

To sum up, the belief that T3 doesn't cross the blood-brain barrier is false. The documentation is far from new. It is high time, then, that we pluck this false belief out of patients' and doctors' frames of reference and dispose of it once and for all.

Timed-Release T3 vs. Plain T3

February 15, 1997

The Question: Are there advantages to using timed-release T3 instead of plain T3?

Dr. Lowe: Many fibromyalgia patients, and clinicians who treat fibromyalgia patients, have contacted the Fibromyalgia Research Foundation requesting information on the advantages of timed-release T3 over plain T3. I've studied the available scientific literature and can find no data indicating any advantage from the use of timed-release T3. I expected this outcome of a literature search. I did so because an understanding of the biochemistry, molecular action, and physiology of T3 doesn't point to an advantage in the use of timed-release T3, except in patients (such as the elder) with extremely fragile heart conditions.

Some clinicians have reported to me that patients using timed-release T3 have a lower incidence of cardiac arrhythmias than patients using plain T3. However, I've performed many series of ECGs on euthyroid patients, and many on hypothyroid patients, who were taking plain T3. Many of these patients were taking supraphysiologic dosages. Rarely have I found arrhythmias. The few I have found were considered, upon cardiology consults, to be associated with underlying cardiac abnormalities that were merely amplified by the T3. Such amplification, however, isn't peculiar to plain T3. We've found similar amplification in a small percentage of fibromyalgia patients taking T4.

In most patients who have excessive cardiac stimulation from taking plain T3, increased heart rate without arrhythmias is the typical finding. I caution clinicians to monitor each patient for idiosyncratic reactions to thyroid hormone, however, regardless of the form used. Cardiac safety should be the foremost concern for patients using any form of thyroid hormone at any dosage. It is vital that proper precautions be taken before patients with compromised cardiac function or underlying cardiac abnormalities begin therapy with any form of thyroid hormone. However, extensive cardiac monitoring of patients treated with our protocol using plain T3 has resulted in no evidence that any advantage would be gained from substituting timed-release T3 for plain T3. While I'm aware of no advantage in the use of timed-release T3, a disadvantage is its higher cost."

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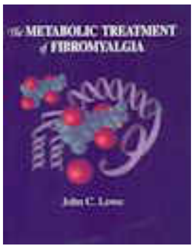

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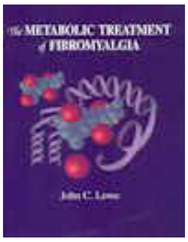

The Metabolic Treatment of Fibromyalgia
by Dr. John C. Lowe

A Reply to Dr. Alex Allinson's Review of Our Protocol & *The Metabolic Treatment of Fibromyalgia*

by Dr. John C. Lowe

November 8, 2002

Latest Updates to drlowe.com

This page contains my reply to Dr. Alex Allinson, a North London medical practitioner in the United Kingdom. Dr. Allison wrote a review of the work of my research team and of my book, *The Metabolic Treatment of Fibromyalgia*. The length of my reply exceeds that of Dr. Allinson's review. While I regret the length, it is necessary to adequately reply to issues raised in his review.

I want to thank Peter Warmingham of Thyroid UK for kindly bringing Dr. Allinson's review to my attention.

Dear Dr. Allinson:

I appreciate your writing a review of my research team's conclusions about fibromyalgia and my book, *The Metabolic Treatment of Fibromyalgia*. I especially appreciate your effort for a particular reason. I believe fibromyalgia patients should decide for themselves which clinical approaches are best for them. They can do so, of course, only when they are aware of the different available clinical approaches. One way for them to become aware is by reading reviews by doctors like you. So, I applaud your efforts to bring to patients' attention our clinical approach.

At the same time, however, I must point out and correct three factual errors in your review. Also, I must comment on a statement you made with which (in slightly modified form) I'm compelled to agree—but with deepest regret for the tragic implications for fibromyalgia patients in the UK.

(1) Regular Blood Tests to Monitor Therapy. You wrote: "Unfortunately, trips to his clinic in Tulsa don't come cheap. Due to the nature of thyroid supplementation, regular blood tests are required to monitor therapy and any improvement."

Trips from the United Kingdom to our Center for Metabolic Health (now in Boulder, Colorado) are expensive. The main expenses are the cost of travel, lodging, and the patient's time away from employment. However, our patients have *no expense whatever* from "regular blood tests . . . required to monitor therapy and improvement." We do initially establish a patient's thyroid status by lab testing. But most of our patients from the United Kingdom bring their lab test results with them, which your National Health Service apparently provides for no out-of-pocket cost to them.

After establishing a patient's initial thyroid status, we do *not* (except when rarely necessary) use further thyroid function testing. That we don't use thyroid test results to guide clinical decisions is a major reason that 85% of our patients fully recover from their fibromyalgia symptoms. As you know, most conventional doctors base their decisions about thyroid hormone therapy on lab test results, especially TSH levels. This is a major reason why so many doctors in the UK fail to help their fibromyalgia patients. Their clinical failure creates the necessity for patients in the UK to work with us in the US to recover through our more effective clinical approach.

(2) Treatment with Thyroxine. You implied in your review that we advise doctors to

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treat patients with T4 (thyroxine). This is patently false. We've *widely* publicized that T4 alone is the least effective thyroid hormone preparation. We've spent many years comparing the safety and effectiveness of the different thyroid hormone preparations—T4 alone, T4/T3 combinations, and T3 alone. Based on the outcome of those comparisons, we can no longer morally justify restricting patients to the use of T4 alone. Some patients respond well to it, but most don't. And *many* patients don't benefit from it at all. If, theoretically, doctors wanted to keep most hypothyroid patients sick, they could do so merely by restricting them to T4 alone. Of course, most doctors want to get their patients well; nonetheless, they unwittingly keep many sick by restricting them to T4.

(3) My "Anecdotal" Conclusions. Referring to me, you wrote, "most of his conclusions are anecdotal." Here you've made the same flagrant error recently made by two other doctors in the United States. I provided a detailed rebuttal to their erroneous description of our work as "anecdotal." In the interest of intellectual accuracy, I trust that you'll read my rebuttal to them. Nonetheless, I explain in the following several paragraphs why your characterization of our conclusions is incorrect.

You will better understand how our conclusions differ from anecdotal ones by reviewing how the typical dictionary defines "anecdotal." According to the *Random House Webster's Unabridged Dictionary*, anecdotal means, "Based on personal observation, case study reports, or random investigations *rather than systematic scientific evaluation*." (Italics mine.) With this definition in mind—especially the phrase I've italicized—consider my description in the next several paragraphs of how my colleagues and I arrived at our present conclusions.

In the late 1980s and early 1990s, my conclusions about fibromyalgia, its underlying causes, and its appropriate treatment were *highly* tentative; they arose—as do *all* scientific hypotheses—as seemingly plausible conjectures.[14][15][16] Having arisen in my mind from clinical observations, my instinct was to reject their veracity and to try to prove the conjectures false. Driven by the conviction that I must be wrong, I scrupulously searched through available scientific knowledge for evidence that contradicted my conjectures. After exhaustive quests repeatedly carried out over several years, I was forced to a conclusion: My conjectures successfully stood up to every attempt I made to refute them. This conclusion (that my conjectures about the cause(s) of fibromyalgia were probably correct) was reinforced by ongoing clinical experiences: My medical colleagues and I were treating fibromyalgia patients with metabolic therapy based on my conjectures about the cause(s) of fibromyalgia. Our treatment protocol at that time was comparatively unpolished. Despite that, we were getting enough patients well so that we knew we understood the underlying mechanisms of at least some patients' fibromyalgia symptoms.

Based on these experiences, I decided that my colleagues and I must do systematic scientific studies to accurately determine why our patients were improving or recovering. Were they improving or recovering because of my enthusiasm from a delusional belief that I was right? Or was I in fact correct?

My colleagues and I were forging a new line of investigation. Our aims were to learn whether fibromyalgia was caused by impaired tissue metabolism and to determine whether patients measurably improved with metabolic treatment centered around the use of thyroid hormone. Like scientists in most new lines of research, we had to learn how best to conduct our studies. To do so, we had to start with open clinical trials—open, *yet highly systematic*. We were rigorously systematic in these open trials for a simple reason: I knew no other way to conduct scientific studies, having been educated and trained in research-oriented behavioral psychology—a field so uncompromisingly systematic in its scientific protocols that by comparison, most clinical research in medicine is slipshod, sloppy, and of doubtful value.

Hence, our initial open trials, although open, weren't mere "personal observation" or "random investigations." Instead, they were *Spartanly systematic*.[1][2][3][4] Only those naive about research methodology and the nature of objective data would label as anecdotal our tentative conclusions from those trials.

We conducted two studies of the thyroid status of fibromyalgia patients. Our conclusions from those studies were based on retrospective analyses of patients' thyroid status at initial clinical intake.[6][7] The conclusions were not based on random investigation or personal observation. They were based on statistical analyses of laboratory test results of unselected patients as they sequentially came into our clinics.

Three of our clinical trials were double-blind, placebo-controlled, cross-over studies.[8][9][10] We conducted these studies with researchers at Baylor University Medical School and the University of Texas Health Science Center.[8][9] The research methodologist, statistician, and clinical researcher at these institutions who participated would strongly object to a critic characterizing as anecdotal our conclusions from these studies.

We also conducted a case-control 1-to-5 year follow-up study. We compared 20 fibromyalgia patients who had gone through our metabolic rehabilitation with 20 scrupulously-matched control fibromyalgia patients.[5] The protocol we used in this study was, again, rigorously systematic. To say our conclusions from this study are anecdotally-derived is like saying formal decisions of the U.S. Supreme Court are based on petty back-porch gossip.

We wrote a paper in which we hypothesized that fibromyalgia patients whose thyroid test results are normal have mutations in the c-*erb*A-ß gene (the gene that codes for the beta thyroid hormone receptor).[11] The paper was published in the world's most respected peer-reviewed, indexed journal on theoretical medical science. One may sincerely believe that our tentative, theoretical conclusion in that paper is anecdotal. But that belief would reflect ignorance of a crucial requirement for the advancement of scientific knowledge—exacting logic-derived hypothesizing based on the available bank of scientific data.

The same ignorance would be obvious if the critic described as anecdotal our conclusion in another of our publications. The paper contains a logical analysis of the available evidence pointing to a 90% incidence of thyroid disease among fibromyalgia patients. The paper was peer-reviewed by two French thyroidologists and France's foremost rheumatology fibromyalgia researcher, Prof. J.B. Eisinger. The paper was further critiqued by scientists at separate meetings in Grenoble and Toulon, France.[12] Finally, it was published in France's major peer-reviewed, indexed rheumatology journal devoted to fibromyalgia.[13] For our conclusion in that paper to survive such scrutiny and end up printed in that journal makes it virtually outside the realm of possibility that the conclusion is a mere offhanded anecdote.

Based on the content of the foregoing paragraphs, I must—as you perhaps understand—vigorously refute your describing our conclusions as anecdotal. Your description is *grossly* inaccurate. It trivializes the years of logical and scientific work of my research team—work continued by means of great sacrifice, and with strict adherence to a self-imposed standard of scientific excellence. If I accomplish nothing more with this reply to your review, it must be this: to emphatically clarify that our conclusions, far from being anecdotal, are as logically sound and scientifically grounded as any current conclusions within medical science.

General Practitioners' Compliance With the Dictates of Endocrinologists. Most mainstream medical doctors aren't privy to the fact that our conclusions about fibromyalgia and thyroid hormone therapy are logically and scientifically based. The reason is simple: Most major medical journals use conventional endocrinologists to review and pass judgment on submitted research reports that deal with thyroid hormone therapy. These reviewers are members of a tightly closed group; with rare exception, unless a dissenting opinion comes from an inside member of that group, the opinion—no matter how scientifically credible—bounces off closed ears. The reviewers seem to think, "Study results that contradict cherished beliefs of our endocrinology specialty *couldn't possibly* be correct! And no report containing such contradictions deserves to be published."

Such prejudicial and irrational thinking by members of that closed group has blocked publication of research findings such as ours in major journals. Moreover, members of the endocrinology specialty have refused to participate in conferences and openly discuss differences in their beliefs and ours. Essentially, they've refused to consider science-based dissenting views and to engage in open and fair debate with credible researchers whose findings contradict some of their beliefs. Their conduct in this matter is clearly outside the boundaries of legitimate science, and it is clearly within the realm of bigotry, dogma, and pseudo-science.

In view of my opinion of the unscientific conduct of the endocrinology specialty, I must address another statement of yours. "I cannot imagine," you wrote, "that *any* British G.P.s would be happy prescribing thyroxine to someone with normal thyroid function test results" (Italics mine). The fact is that *some* British G.P.s do admirably treat some patients with thyroid hormone despite what you incorrectly call "normal" thyroid test results. So I can't agree with your absolutistic statement about "*any* British G.P.s." But when rephrased to more accurately say "most British G.P.s, I'm afraid you are quite correct—*tragically so!*

One reason you're correct is that, as Prof. Linus Pauling said, "Of all the professions, the medical profession is the one in which the individual practitioners do the smallest amount of thinking for themselves."[17] Instead, conventional physicians accept without question most any pronouncement (despite clear evidence of its absurdity) from those they consider *authorities* in specialties other than their own. General practitioners who permit the endocrinology specialty to think for them absorb into their belief systems several false conclusions about thyroid hormone therapy—conclusions based on almost incomprehensibly bad science and huge financial incentives from corporations that market thyroxine and TSH assays; conclusions that keep millions of patients sick and end the lives of many prematurely. The misery and ruined lives of these patients, and the avoidable early deaths, could come to a halt—if only general practitioners would resume thinking for themselves as they probably did before entering the medical profession.

I understand, of course, the two main reasons that most physicians do so little thinking for themselves. The first reason is understandable and justifies sympathy toward the physicians. As I pointed out in 1998 at the University of Texas Health Science Center, we doctors are now deluged with new scientific information. Keeping up with even a thin sliver of it is a burden. Because of this, we often must depend on the opinions of other doctors who, presumably, keep up on new information in their specialties.

The second reason doctors generally don't think for themselves is also understandable. Despite being understandable, this reason justifies the contempt in which millions of patients now hold mainstream medical doctors. Regarding patients' needs for safe and effective thyroid hormone therapy, most general practitioners comply without question with the dictates of the endocrinology specialty. A major reason general practitioners comply is their fear of power politics. Violate the endocrinology specialty's mandates for the diagnosis and treatment of hypothyroid patients, and regulatory agencies (such as the UK's General Medical Council) may impose Draconian punishment—as in the cases of Dr. Barry Peatfield and Dr. David Derry. The threat of these agencies punitive actions—usually prompted by the endocrinology specialty—intimidates general practitioners into obsequent compliance. And this thuggery-induced compliance serves well the financially lucrative relationship between the endocrinology specialty and its corporate bedfellows. I firmly believe that for the endocrinology specialty, science—and bad science at that—serves as little more than a pretense for imposing the specialty's false beliefs on the public and other doctors in the service of power and profit. And mainstream medical doctors, largely unwittingly, abet this diabolical enterprise. They do so by failing to effectively use the cortical gray matter with which most are well-endowed, which otherwise would lead them to defy the endocrinology specialty's mandates that are derived from its lucrative but false beliefs about thyroid hormone therapy.

Regrettably, then, but for reasons different from your own, I concur with your rephrased statement, "I cannot imagine that [most] British G.P.s would be happy prescribing thyroxine to someone with normal thyroid function test results."

Conclusion. As I said at the outset, I appreciate your having written a review of my research team's work and *The Metabolic Treatment of Fibromyalgia*. The book is, of course, huge, and I applaud you for taking on the formidable task of reading enough of it to report its contents to your readers. I sincerely hope you find it in no way disquieting for me to note and correct the three factual errors in your report. (Similarly, I hope you take no offense at my reason for agreeing with your opinion that most British general practitioners won't "be happy prescribing thyroxine to someone with normal thyroid function test results.") The book's size will inevitably compel some reviewers to minimize their toil by presuming rather than verifying some views I expressed in the book, and I sympathize with this. I hope in turn, however, that those reviewers, yourself included, can sympathize with the necessity of my correcting resulting errors that may turn up in their reviews.

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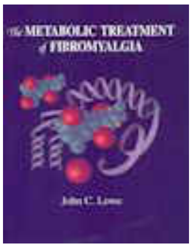

The Metabolic Treatment of Fibromyalgia

Acupuncture: Is it an Effective Treatment for Fibromyalgia?

Reply to a Question by Dr. John C. Lowe

September 7, 2005

Question: I read in a newspaper article that acupuncture cures fibromyalgia. Doesn't that show that your idea that fibromyalgia is caused by hypothyroidism is wrong?

Dr. Lowe: Perhaps you did read that acupuncture "cures" fibromyalgia. If so, what you read is wrong. Of course, media people commonly misrepresent the contents of press releases they receive from researchers and institutions, and you may have read one of these misrepresentations.

The story you read was probably based on a recent press release sent out by the Mayo Clinic. The subject of the press release was a study conducted by Dr. David Martin. He reported the results at the 11th World Congress of the International Association for the Study of Pain in Sydney, Australia.[1] Dr. Martin is a Mayo Clinic* anesthesiologist and the study's lead investigator.

You said you read that acupuncture cures fibromyalgia. But here is what the press release actually said about the effects of acupuncture: ". . . the patients saw *improvement* in symptoms," with fatigue and anxiety improving most. Note that the release did *not* say the patients were *relieved or freed* of their symptoms; instead, they saw *improvement*.

Logically, improvement could entail full recovery, but the release didn't say the patients no longer met the criteria for fibromyalgia. In fact, Dr. Martin wrote, "Their physical function did not increase even though the patients were less tired and felt less pain." The patients obviously didn't fully recover. If they had, then surely the release would have emphasized it. Improvement, then, meant that acupuncture only reduced the intensity of some of the patients' symptoms.

Dr. Martin wrote that "acupuncture is one of the few things *shown to be effective* for these symptoms." (Italics mine.) However, that acupuncture is effective at all for fibromyalgia patients is far from conclusive. After all, another 2005 study of acupuncture treatment for fibromyalgia showed that it worked no better than "sham" (pretend) acupuncture.[5]

But assuming Dr. Martin is correct that acupuncture was effective in his study, we must be careful to deduce what he meant by the term "effective." The term could mean anything from fully relieving to barely reducing patients' symptoms.

I am often critical of fibromyalgia (and other) researchers for failing to precisely formulate their statements. This criticism is no mere quibble. In Dr. Martin's case, some fibromyalgia patients may mistake his term "effective" to mean that acupuncture can fully free them of fibromyalgia.

But clearly, patients in the study got a *palliative*—not curative—effect from the acupuncture.

Dr. Martin also wrote, "Our study was performed on patients with moderate to severe fibromyalgia. It's my speculation that if acupuncture works for these patients with recalcitrant fibromyalgia—where previous treatments had not provided satisfactory relief—it would likely work for many of the millions of fibromyalgia patients."

Many fibromyalgia patients may get palliative benefits from acupuncture. I say "may" because of the other 2005 study that showed acupuncture *per se* was not effective.[5] We don't for a second suggest, however, that fibromyalgia patients not avail themselves of possible palliative benefits from any form of treatment, including acupuncture. In fact, we always give fibromyalgia patients a particular piece of advice: use most any form of treatment that makes life tolerable for you until you can recover with metabolic rehab. One should not forget, though, that at best, the benefits of acupuncture are palliative. By definition, palliative treatments lessen the severity of symptoms without relieving them; the improvement is temporary and less-than-complete. Because of this, palliative treatments should not substitute for patients undergoing metabolic treatment that may *fully* free them from their symptoms.

The press release quotes Dr. Martin as saying, "there's no cure available." This absolute statement implies that he has omniscient knowledge of the treatment studies of fibromyalgia. If he did, however, he could not be responsible and make this statement. In his defense, however, our major studies were blocked from publication in journals that have major indexing. Partly because of that, he most likely is unaware of our studies. Nonetheless, the studies exist. And in line with those studies, theoretical deductive science shows that fibromyalgia is a disorder of hypometabolism underlain mainly by too little thyroid hormone regulation. We will soon make this known on the broadest scale so that investigators such as Dr. Martin are aware of it.

The bottom line is this: acupuncture may give some fibromyalgia patients palliative benefits, as do massage therapy and chiropractic care. Patients and clinicians should keep in mind, however, a statement by acupuncture researcher Dr. Haiko Sprott that I quoted in *The Metabolic Treatment of Fibromyalgia*:[6,p.921] "Acupuncture is useful only when used as an adjunct within a comprehensive therapeutic program. The clinician is cautioned not to use acupuncture as the only remedy.[3]"

*I must say that personally, I hold in the highest suspicion any study announcement coming from the Mayo Clinic. When some doctors at an institution have been found guilty of science fraud, I forever distrust the institution's competence or willingness to uphold integrity in science.

As Professor Linus Pauling reported,[2,pp.233 & 312-313] in 1985 six of Mayo's doctors committed science fraud. They did so by intentionally falsely reporting (in the *New England Journal of Medicine*[4]) that high-dose vitamin C had no value for advanced colon and rectal cancer patients. In my mind, the Mayo doctors' fraudulent action demeaned the reputation of the Clinic. It also raised serious doubts about the *New England Journal of Medicine*'s internal controls for insuring honesty and accuracy in medical science reporting. But even worse, popularization of the Mayo doctors' fraudulent report may be responsible for worsening the misery and shortening the lives of many patients whom high-dose vitamin C therapy may have helped.

This statement of my distrust is directed at the Mayo Clinic and the *New England Journal of Medicine.* It is not directed at Dr. David Martin personally or professionally.

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drlowe.com
Metabolic Health

Fibromyalgia, Hypothyroidism, Thyroid Hormone Resistance

Commentary
Dr. John C. Lowe

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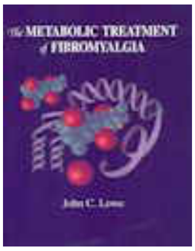

The Metabolic
Treatment
of Fibromyalgia
by Dr. John C. Lowe
Readers' Comments

New Book
Your Guide to
Metabolic Health

Advocate of Dr. Paul St. Amand Apologizes for Libelous Accusations

Comments by Dr. John C. Lowe

Below are full copies of several communications that occurred between June 22 and July 9, 2002. The first two and the fifth are e-mails. The third and fourth are letters sent through the U.S. mail for legal purposes. The first e-mail below is from Mrs. Sharon Jungert, an advocate of Dr. Paul St. Amand. Her e-mail initiated the subsequent e-mails and letters. Mrs. Jungert's original e-mail contains false and libelous statements about me. Because of this, I took action to persuade her to publicly retract the accusations she made in the e-mail.

In publishing the communications here, I have no wish to embarrass Mrs. Jungert. Instead, my purpose is to deter others who are prone to unjustly malign chiropractic physicians. Case law shows that the consequences for those who malign chiropractic physicians can be extremely costly. On the other hand, to avoid such costs, some people, such as Mrs. Junkert, find that they must publicly apologize and admit they had no grounds for their libelous accusations. With the publication here of these communications, I now consider this unfortunate incident closed.

Note: It's customary to write "sic" after a word or statement that is incorrect but presented as the author wrote it. The number of mistakes in some of the e-mails and letters below are so numerous that I've chosen not to note them with "sic." However, the content of the e-mails and letters, including errors, are presented precisely as they were written by the authors.

Libelous E-mail from Sharon Jungert

Subj: Chriopractic Quack - Dr. Lowe D.C.
Date: 6/22/2002 8:02:59 AM Mountain Daylight Time
From: tgogil@attbi.com (Gil Jungert)
Reply-to: tgogil@attbi.com (Gil Jungert)
To: DrJohnLowe@aol.com (DR Lowe)
CC: fmsnurse@aol.com (Claudia Marek), xxxxx@Williams.com, xxxxx@earthlink.net, xxxxx@mindspring.com, xxxxx@optushome.com.au [Mrs. Jungert copied this e-mail to five people, one of whom was Claudia Marek, Dr. St. Amand's nurse. I have deleted the names and e-mail addresses of the other four people to protect their privacy. Dr. John C. Lowe]

After reviewing the question and answers from the following web site here is my response to what I consider a Chiropractic Quack.

Look at this :- http://www.drlowe.com/QandA/askdrlowe/guaifenesin.htm

---

Dr. Lowe D.C.: I could not agree more with Dr. Bernard Lown Ref: THE LOST ART OF HEALING by Bernard Lown, M.D. He so eloquently describes Doctors like you, Dr. Lowe, who are clearly out to make millions of Yankee dollar by preying on your 22,000 un-suspecting patients who are in pain. Your reference to good doctors like Dr. Bernard Lown is clearly an attempt to hitch your fallen star to his rich credentials. Dr. Bernard Lown stated:

> "No significant social transformation results from a single or simple cause. Reflecting on forty-five years of medical practice, I see that something vital appears to be vanishing. It seems to me that medicine has indulged in a Faustian bargain. A three- thousand-year tradition, which bonded doctor and patient in a special affinity of trust, is being traded for a new type of relationship. Healing is replaced with treating, caring is supplanted by managing, and the art of listening is taken over by technological procedures. Doctors no longer minister to a distinctive person, but concern themselves with fragmented, malfunctioning biologic parts. The distressed human being is frequently absent from the transaction."

Yes, your Web site is full of errors and mis-statements, and blatant un-truths. The JAMA 2000 Jul 26;284, reference by Barbara Starfield you quoted is totally in error.

When you reference a "Well Designed Study" I can only assume that is in reference to the Oregon Study by Dr. Robert Bennett. In that study critical elements were not addressed. Salicylates and their impact on Guaifenesin was not included or addressed.

A good place for you to begin your studies would be Dr. R. Paul St. Amand's web site, http://www.guaidoc.com/, and the article; "Refuting the Oregon Study", available at his web site and it clearly addresses the deficiency of not considering the effects of Salicylates on Guaifenesin. Quote, "Patients have been routinely cautioned to avoid aspirin, as aspirin compounds block the uricosuric effect of the medications. We had also discovered that aspirin rendered the medications ineffective in treating Fibromyalgia".

Dr. Lowe, Being the director of research of the Fibromyalgia Research Foundation, you should not malign Dr. R. Paul St. Amand's Guaifenesin Protocol by saying, "Dr St. Amand's beliefs, which I judge to be Scientifically False". You are not being professional. Which of your credentials allow you to "judge" anyone's work? Not even mine, 'a lay person', with a brain. My understanding is, to be a judge you must be omniscient? Are You?

Dr Lowe, how long have you suffered from Fibromyalgia? I do know that Dr R. Paul St. Amand, and his family suffered for years before finding an answer to Fibromyalgia, using Guaifenesin. My Daughter and I both suffer from Fibromyalgia and are both responding nicely to the point my Daughter has proclaimed "Its a miracle", from the Guaifenesin Protocol. I await your timely response.

Best Regards, Sharon J. 1 year on 1800mgs Guai, 62yrs FMS 30yrs

Reply to Sharon Jungert by Dr. St. Amand's Nurse, Claudia Marek

Claudia Marek, Dr. St. Amand's nurse, was among the people to whom Mrs. Jungert sent her libelous e-mail. Claudia replied to Mrs. Jungert with the following e-mail. Claudia sent the reply not only to Mrs. Jungert, but also to the other people to whom Mrs. Jungert had sent her libelous e-mail. The text of Claudia's e-mail suggests that she failed to send me the full content of the e-mail she sent to the others.

Subj: Re: Chriopractic Quack - Dr. Lowe D.C.
Date: 6/22/2002 4:14:01 PM Mountain Daylight Time
From: FMSNURSE@aol.com
To: tgogil@attbi.com, DrJohnLowe@aol.com
CC: xxxxx@Williams.com, xxxxx@earthlink.net, xxxxx@mindspring.com, xxxxx@optushome.com.au [Claudia copied this e-mail to four people. I have deleted their names and e-mail addresses to protect their privacy. Dr. John C. Lowe]

> Or, go to www.quackwatch.com to read about Wilson's Disease and other such things . . . . .Claudia Marek

When I first read Claudia's e-mail reply to Mrs. Jungert, I assumed that through it, she had climbed onto Mrs. Jungert's "Dr.-Lowe-is-a-quack" bandwagon. To me, this was implied by Claudia's statement, "Or, go to www.quackwatch.com to read about Wilson's Disease *and other such things*." (Italics mine.) Discerning Claudia's intention, however, was difficult. It was difficult because, as readers can see, what preceded, "*Or*, go to . . " (italics mine) was deleted from the e-mail Claudia forwarded to me. Some statement we're not privy to appears to have preceded the text that remains in the e-mail she forwarded to me. At minimum, I feel that Claudia's e-mail fans the flames of the false sentiment among some that I'm a quack. Regardless, as I spelled out to Claudia in my final e-mail to her, she narrowly eluded the deeper involvement in this case that Mrs. Jungert failed to escape.

Had I filed a libel suit against Mrs. Jungert, it's highly probable that I would have won it. She libeled me on two counts: First, by accusing me of quackery, and second, by accusing me of trying to make millions of dollars by "preying on" unsuspecting pain patients. I could easily prove both of these accusations to be false. In addition, she e-mailed her defamatory statements to five other people. This constituted "publishing" her statements, thus qualifying them as libel.

Moreover, Mrs. Jungert put herself in a highly unfavorable position regarding a libel suit. Ordinarily in a libel suit, being awarded general damages (those *expected* to result from the libelous act) depends upon the libeled person proving that he's suffered special damages—those (such as harm to one's professional reputation) that are computable in money. Among the exceptions to this rule is one relevant to this case—"*per se* defamation." Mrs. Jungert accused me of having a characteristic (being a quack) that detracts from the professional qualities required of licensed chiropractic physicians and board certified pain management specialists. My professional record, however, clearly shows that I've exhibited all qualities required of such physicians and specialists —including not being a quack. Hence, her accusation of quackery is false and constitutes *per se* defamation. This means that, had I won a suit against her, Mrs. Jungert would likely have had to pay me larger general damages without my having to prove special damages.

Based on this legal position favorable to me, I promptly took steps to have Mrs. Jungert do one of two things: (1) publicly apologize for her libelous accusations and admit she had no grounds for them, or (2) face aggressive legal action for libel. I presented these options to her in the following letter.

Letter of Demand to Sharon Jungert

July 2, 2002

Sharon Jungert
3061 Wellington Ave
Grand Junction, CO 81504-5686

Dear Mrs. Jungert:

In your e-mail to me and several other people dated 6/22/2002, you flagrantly and egregiously libeled me. The specific libelous statements you wrote include the title of your e-mail: (1) "Chriopractic Quack - Dr. Lowe D.C." Also included are:

> (2) "After reviewing the question and answers from the following web site here is my response to what I consider a Chiropractic Quack."
>
> (3) "Dr. Lowe D.C.: I could not agree more with Dr. Bernard Lown Ref: THE LOST ART OF HEALING by Bernard Lown, M.D. He so eloquently describes Doctors like you, Dr. Lowe, who are clearly out to make millions of Yankee dollar by preying on your 22,000 un-suspecting patients who are in pain. Your reference to good doctors like Dr. Bernard Lown is clearly an attempt to hitch your fallen star to his rich credentials. "

It is clear to me that your intention in making these libelous statements was malicious and that you intended to dishonor me and generate public contempt for me.

Judging from your email, you are not a well-educated person, and on that basis, I assume you are ignorant of libel law and of the backbreaking expenses involved in defending a libel law suit. I assume, too, that you have had no experience with the sense of invasion that usually accompanies the court-ordered exposure of the defendant’s financial and other private matters in the process called "pre-trial discovery." On the assumption that you are ignorant about these matters but would prefer to avoid them, I am going to give you the opportunity to sidestep them and redeem yourself. You can do so by writing an apology to me in which you *specifically recant the three quoted libelous statements I listed above*, stating that you apologize for making the three statements and that you have no evidence that any of the statements is true. You will also have to provide me with a release letter giving me permission to use your written apology in any way I choose.

If you opt not to write an apology and release, I will ask my attorney to send you a letter of demand. In that letter, he will demand a cash out-of-court settlement from you plus his legal fees that will have accumulated as a result of your libelous statements about me. If you decline that demand, I will ask him to follow through with legal proceedings against you and file a libel suit.

Having spent many years serving as an expert witness in depositions and courtrooms, I am entirely comfortable with litigation and am an enthusiastic and aggressive litigant. This being the case, unless you have deep pockets and an extraordinarily strong character in standing up to the severe stress of a suit at law, you will want to act promptly and retract in writing your three libelous accusations.

If I do not receive a response from you within ten days of the date of this letter, I will ask my attorney to aggressively proceed with the steps I have described above.

Resolutely,
Dr. John C. Lowe
cc: Randy Holmes, J.D.

Letter of Release From Sharon Jungert

July 9, 2002

Dr John C. Lowe
1800 30th Street Suite 217A
Boulder CO 80301

Letter of Release

I, Sharon Jungert residing at 3061 Wellington Ave, Grand Junction Co 81504, grant to Dr. John C. Lowe the rights to use this letter [see letter below], all rights and privileges. This letter of release applies to the use with the full contents only of the Letter of Apology, dated July 9, 2002, in any way He chooses. Sharon Jungert

Letter of Apology From Sharon Jungert

July 9, 2002

Dr John C. Lowe
1800 301h Street Suite 217A
Boulder CO 80301

Dear Dr. Lowe,

In response to your letter dated July 2, 2002, concerning my email dated 6/22/2002, where you feel that I egregiously libeled you. I am going to address the three items you have outlined as follows:

I retract and sincerely apologize for making the three following statements that use any derogatory terms. I specifically recant the following 3 statements, quoted from your letter of July 2, 2002. I have no evidence as to the veracity of these statements.

1) Title in the e-mail, "Chriopractic Quack - Dr. Lowe D.C."

2) "After reviewing the question and answers from the following web site here is my

response to what I consider a Chiropractic Quack".

3) "'Dr. Lowe: I could not agree more with Dr. Bernard Lown Ref: THE LOST ART OF HEALING by Bernard Lown, M.D. He so eloquently describes Doctors like you, Dr. Lowe, who are clearly out to make millions of Yankee dollar by preying on your 22,000 un-suspecting patients who are in pain. Your reference to good doctors like Dr. Bernard Lown is clearly an attempt to hitch your fallen star to his rich credentials".

Again, **I sincerely apologize** for these statements. I truly meant you no harm, nor was it my intent to libel you.

I was mad at the world for giving me this dread disease, Fibromyalgia. These statements were made by me after suffering from Fibromyalgia for the past 30 years. Only in the past 1 1/2 years have I found some relief from these pains and the relief is not continuous.

Yours truly, Sharon Jungert

E-mail to Individuals Mrs. Jungert Copied Her Libelous E-mail to

Subj: Sharon Jungert's libelous accusations against me
Date: 8/5/2002 5:49:10 PM Mountain Daylight Time
From: Jlowe55555
To: [I send this e-mail to all the people Mrs. Jungert sent her libelous e-mail to. I copied it to Mrs. Jungert, Claudia Marek, and Dr. Paul St. Amand.]

On June 22, 2002, you received an e-mail from Mrs. Sharon Jungert in which she made libelous accusations against me. I wrote to Mrs. Jungert and pointed out the legal ramifications of her accusations. In response, she wrote a letter of apology to me for which I am grateful. However, because Mrs. Jungert shared her libelous e-mail with you, and because it was circulated on at least one fibromyalgia news group, I have posted all communications relevant to her e-mail to the following web page: http://www.drlowe.com/jcl/comentry/libel.htm

I emphasize that I have *not* posted the communications to the web page to cause Mrs. Jungert embarrassment. Instead, I've done so for the same reason that many libel victims file law suits—to deter others from libeling the plaintiff. My intention is to deter others from libeling chiropractic physicians in general and me in particular.

I now consider this unfortunate incident closed, and I extend my apologies to Mrs. Jungert for any embarrassment she might suffer from my posting the communications to our website.

Sincerely,
Dr. John C. Lowe

E-mail to Dr. St. Amand's Nurse, Claudia Marek, and to Dr. Paul St. Amand

Subj: From Dr. John C. Lowe
Date: 8/5/2002 3:28:05 PM Mountain Daylight Time
From: Jlowe55555
To: FMSNURSE@aol.com (Claudia Marek, RN)
CC: FMSDoc@aol.com (Paul St. Amand, M.D.)

Dear Claudia,

You might find interesting the outcome of Mrs. Sharon Jungert's libelous accusations against me contained in her e-mail to you dated June 22, 2002. The URL to the outcome is http://www.drlowe.com/jcl/comentry/libel.htm.

I should point out that you narrowly escaped serious entanglement in this incident. The copy of your e-mail reply to Mrs. Jungert that I received was truncated. My legal counsel advised that I demand from you the full content of the e-mail. I suspect that if

I had, the text missing from your e-mail would have necessitated that you, like Mrs. Jungert, write a formal public letter of apology to me. It will be prudent of you, Claudia, to understand something: My criticisms of Dr. St. Amand's beliefs about fibromyalgia have been scholarly and entirely within the bounds of the responsibility of a practicing scientist. I graciously accept similar criticisms of my beliefs by others—scientists, clinicians, and patients. But I absolutely will not brook the sort of defamation of character exemplified by Mrs. Jungert's libelous e-mail, and I will take aggressive legal action against anyone who engages in it against me.

Sincerely,
Dr. John C. Lowe

Commentary
Dr. John C. Lowe

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Letter to Gov. George W. Bush About Dieticians	St. Amand Advocate Apologizes for Libel
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Doubts About Self-use Device for Measuring Metabolic Rate
T3 Enters the Brain: Summary	T3 Enters the Brain: Details

New Studies Refute an Old Objection to T3 Therapy

Dr. John C. Lowe
August 17, 2005

In 2002, a Portuguese molecular biologist, Dr. Joana Palha, reported study findings that, although not intended to, show that an argument for using T4 alone is false. The findings should change the beliefs and clinical practice of many doctors, enabling more hypothyroid patients to get effective treatment.

Since the 1950s, some thyroid researchers believed there was only one way thyroid hormone got from the blood into the brain: by binding to a protein called "transthyretin" (trans’-th§-r‘’-tin). Transthyretin is one of three proteins that bind and transport thyroid hormone. The main protein is "thyroxine-binding globulin" and the other is "albumin."

Cell membranes have sites that strongly bind transthyretin. The binding sites are probably transthyretin receptors that are instrumental in delivering thyroid hormone into cells.[4]

The transthyretin that transports thyroid hormone in the blood is manufactured by the liver. Transthyretin that transports thyroid hormone from the blood into the brain is produced in a brain structure called the "choroid plexus." The choroid plexus is a complex outgrowth of blood vessels. It’s situated just above the brain stem and below the brain’s fluid containing cavities called "ventricles." The plexus produces and secretes the fluid, called "cerebrospinal fluid," that the brain and spinal cord float in.

Thyroid hormone travels to the choroid plexus through the blood. When the hormone encounters the transthyretin the plexus has produced, the hormone binds to it. Then the protein transports the hormone into the brain.

T3-Binding to Transthyretin. In the 1950s, limited information led some researchers to conclude that transthyretin only transports T4 into the brain. Based on this conclusion, they believed that brain cells get their T3 only by converting T4 to T3. Some doctors adopted these two beliefs. And based on the beliefs, they wouldn’t let their patients use T3 alone. These false beliefs probably contributed to conventional doctors’ rigid use of T4-replacement (patients’ use of T4 alone with their dosages adjusted by their TSH levels). All of this happened despite studies in the 1950s and early 1960 that showed T3 alone was highly effective for patients who failed to benefit from T4 alone or T4/T3 therapy.

Let me illustrate the types of problems that resulted from doctors holding these false beliefs. I used to co-treat patients with a neuropsychiatrist in Houston, Texas. More than once, he expressed frustration at an experience he occasionally had. After he prescribed T3 for depressed and cognitively-impaired hypothyroid patients, endocrinologists would switch them to T4-replacement. The endocrinologists would argue that without taking T4, the patients’ brain cells wouldn’t have enough T3. But soon after being switched to T4, their depression and cognitive dysfunction returned. So, when the patients went back to the neuropsychiatist to complain, he switched them

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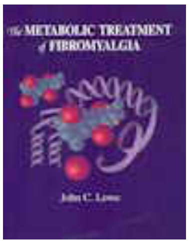

The Metabolic Treatment of Fibromyalgia
by Dr. John C. Lowe
Readers' Comments

back to T3. Quickly, their depression and cognitive dysfunction cleared up again.

At that time, it appeared to the neuropsychiatrist and me that transthyretin must transport T3 as well as T4 into the brain. We assumed this because we trusted that the researchers were right about thyroid hormone getting into the brain only by piggybacking on transthyretin.

Dr. Pilha, author of the Portuguese studies I cite here, appears to agree with the researchers and doctors who believe that transthyretin delivers only T4 into the brain. She recently wrote that transthyretin "binds virtually no T3."[3,p.1293] She then went further, stating that transthyretin "is not a T3 carrier."[3,p.1296]

But other researchers contend that transthyretin binds and transports both T4 and T3.[1][2] Some of these investigators have measured how readily T4, T3, and T2 bind to transthyretin. By far, T4 binds most strongly to the protein. T3 binds to it but with 10-times lower affinity than T4. T2 also binds to transthyretin, although with 100-times less affinity than T4.[6] (An enzyme converts T3 to T2 when it removes one of T3's three iodine atoms.)

The conclusion that T3 binds to transthyretin is consistent with findings of other studies. Researchers have documented that T3 passes the blood-brain barrier and enters the brain.[9][10][11]

One study showed that how readily T3 enters the brain depends on the shape of its molecule. The molecule comes in two shapes, right and left. We call the right-handed molecule dextro-T3 or DT3, and the left-handed molecule levo-T3 or LT3. LT3 enters the brain about three times more readily than DT3.[7]

The T3 in products such as Cytomel and Cynomel is LT3.[8] Even in the absence of transthyretin, LT3 (along with less DT3) still readily passes the blood-brain barrier and enters the brain.

New Studies. Some doctors, as I wrote above, long denied patients the use of T3 alone because they thought that transthyretin only carries T4 into the brain. But whether the protein carries only T4 or both T4 and T3 into the brain has become an irrelevant question in view of the new studies cited by Dr. Pilha.

The researchers who conducted the studies found that transthyretin isn’t essential for T4 or T3 to get into the brain, at least not in mice. Nor is transthyretin necessary for a normal T3 concentration in brain cells. Dr. Pilha wrote that this is now shown "conclusively" by studies of mice whose cells produce no transthyretin at all.[3,p.1292] Despite the mice having no transthyretin, they have normal amounts of T3 in their brain cells.[3][12][13]

Proteins that transport thyroid hormone through the blood also aren’t essential for T4 and T3 to enter tissues other than the brain. Nor are the proteins necessary to having a normal concentration of thyroid hormone in the cells. For example, humans who have no "thyroxine-binding globulin" (the major transport protein in humans) still have normal thyroid hormone regulation. The same is true of rats that have no albumin, which is their major thyroid hormone binding protein.

Some researchers used to disagree with the "free hormone hypothesis," which states that it’s the free thyroid hormone in the blood that’s important to normal biological function. These new findings, however, show that the free hormone hypothesis is correct.[3]

Conclusion. In a critique I wrote in 2004,[5] I documented some disturbing findings about T4-replacement: in five studies, it left hypothyroid patients suffering from hypothyroid symptoms.[14][15][16][17][18] And in one study, patients on T4-replacement used more drugs and had an increased incidence of potentially fatal diseases.[18]

Our long line of research shows that some patients with too little thyroid hormone regulation don’t benefit at all from T4-replacement or from T4/T3 combination therapy. Virtually all these patients, however, improve or recover with high enough doses of T3 alone.

On such patients' behalf, we need to get word of these studies out to their doctors. I hope that doctors who've falsely believed that the brain gets T3 solely from T4 will consider the treatment implications of the study results. If so, perhaps they'll then allow their patients who respond poorly to T4-replacement or T4/T3 therapy to switch to T3 alone, the only approach likely to work for them.

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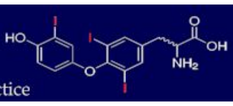

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Criticism

Stability, Effectiveness, and Safety of Desiccated Thyroid vs Levothyroxine: A Rebuttal to the British Thyroid Association

Dr. John C. Lowe*

*Director of Research, Fibromyalgia Research Foundation
Contact: Dr. John C. Lowe drlowe@drlowe.com

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Abstract. In 2007, an Executive Committee (the Committee) of the British Thyroid Association (BTA) published a document in which it concluded that levothyroxine is safer, more stable, and more effective than Armour Thyroid. By extension, the conclusion also applies to other desiccated thyroid products, such as Erfa Thyroid. Enough evidence is available, however, to conclude that T_4/T_3 therapies with either synthetic hormones or desiccated thyroid are safer and more effective than T_4 replacement, and that desiccated thyroid is more stable than levothyroxine products. The Committee mentioned clinical trials that directly bear on its conclusions, but it did not include any of these in the reference section of its document. Instead, it referenced a review of the clinical trials by Escobar-Morreale et al. and a meta-analysis of the trials by Grozinsky-Glasberg et al. These two publications, however, deal with synthetic T_4/T_3 therapies, not desiccated thyroid. Both publications contain factual errors and unbalanced presentations of data, excluding or limiting data favorable to T_4/T_3 therapies. Specific examples from the publications are included in this rebuttal. The unbalanced data presentations and factual errors of Escobar-Morreale et al. and Grozinsky-Glasberg et al. may have influenced the Committee's conclusions. Nonetheless, the Committee's document contains false statements and unbalanced presentations of data independent from those in the other authors' publications. Specific examples are included in this rebuttal. The Committee, the BTA, Escobar-Morreale et al., and Grozinsky-Glasberg et al. are all called upon to correct their false statements of fact as well as their unbalanced presentations of data relevant to their conclusions.

Keywords. Armour Thyroid • British Thyroid Association • Levoxyl • Desiccated thyroid • Erfa Thyroid • FDA • Levothyroxine • Synthroid

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Introduction: Attacks on Desiccated Thyroid

In February 2007, an Executive Committee of the British Thyroid Association (the Committee) published a document in which it denounced Armour Thyroid (Armour). Armour Thyroid is a brand of natural desiccated thyroid that contains four parts T_4 to one part T_3, that is, a ratio of 4 to 1 (4:1). Whether the Committee intended it or not, its arguments against Armour also apply to other brands of desiccated thyroid, including Erfa Thyroid. Because the arguments apply to all such products, in this rebuttal I subsume and refer to all such brands as desiccated thyroid except when particular passages are specific to Armour. In its document, the Committee, as well as opposing the use of desiccated thyroid, also advocated T_4 replacement as the preferable treatment for hypothyroidism.

The basic issues raised by the Committee were (1) the stability of desiccated thyroid, and (2) its safety and (3) effectiveness as a form of treatment for hypothyroid patients. Considerable evidence that bears on these issues is readily available. Yet the Committee cited virtually none of it. In this rebuttal, I cite the evidence they left out of their document. When faced squarely and considered without prejudice, that evidence leads to conclusions diametrically opposed to those of the Committee.

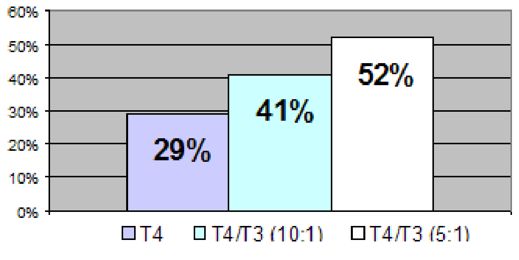
The medical literature contains at least twenty reports of studies in which researchers compared the effectiveness and safety of different thyroid hormone therapies.[7][10][15][16][22][23][24][25][26][29][31][32][33][36][39][40][41][42][44][45] Among the therapies compared in the studies were T_4 alone, desiccated thyroid, and combined synthetic T_4/T_3. Instead of referencing these studies, however, the Committee cited only two papers in which authors reviewed the most recent studies that compared T_4 monotherapy to synthetic T_4/T_3. One of those papers is a review of the studies by Escobar-Morreale et al.,[17] and the other is a report of a meta-analysis by Grozinsky-Glasberg et al.[18]

In this paper, I critically dissect relevant parts of the two papers cited by the Committee. I also show that both papers contain errors that misinform readers who take the authors' statements at face value. Members of the Executive Committee appear to be among the misinformed. I include citations below that indicate that the Committee accepted without question and reiterated false statements of the authors of the two papers. Possibly as a result of this, but apparently for other reasons, the Committee's document contains falsehoods that I cite below. As will be obvious to readers, only if the falsehoods were true could the Committee validly deduce its conclusions about T_4 replacement and desiccated thyroid. But the evidence I present shows that the falsehoods are indeed false.

Issues Raised by the Committee of the British Thyroid Association (BTA)

The Committee contends that T_4 is more stable, safer, and more effective than desiccated thyroid. This proposition, however, is a mere presumption, one that is refuted by evidence that I present below. The Committee bulwarks its proposition only with an unbalanced presentation of some evidence, and false laims about other relevant evidence.

Figure 1. Patients in Each Group Satisfied with the Form of Treatment (Appelhof et al Study.[18])

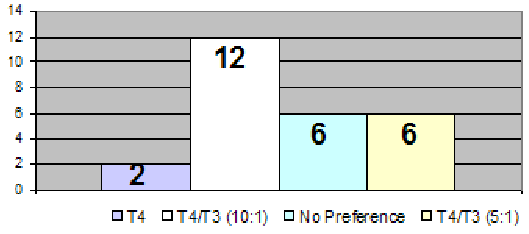


As I document below, contrary to the conclusions of the Committee, the evidence shows that compared to desiccated thyroid, T_4 is actually *less* stable. Moreover, thyroid hormone *replacemen*t therapies (dosages of thyroid hormone that keep the patient's levels of the TSH within its current—but often revised—reference range), including T_4 replacement and T_4/T_3 replacement, are not effective for many patients and because of this, potentially harmful to them.

Because of its documented ineffectiveness for many patients and consequent potential harm, T_4 replacement should be abandoned as the thyroid hormone therapy of choice. Clinicians should preferably most often prescribe desiccated thyroid, synthetic T_4/T_3, of synthetic T_3 alone; and the dosages should best be larger than replacement dosages.

I base this recommendation on several findings: (1) hypothyroid patients have *long* used desiccated thyroid *safely and effectively*, (2) many studies show desiccated thyroid to be at least as effective as T_4 replacement, and (3) two studies showed that patients who used T_4/T_3 therapy in a 5:1 ratio (close to the 4:1 ratio in desiccated thyroid) had no adverse effects—*while patients using T_4 alone have adverse effects!*—and *were more satisfied with the combination therapy than with T_4 alone* (see Figures 1 and 2).

Figure 2. Number of Patients of 28 Who Preferred a Form of Treatment (Escobar-Morreale et al.[16])



Invalid Conclusion

When Bunevicius et al. reported improvement in cognitive function after patients substituted 12.5 µg of T_3 for 50 µg of their T_4 dosage,[7] other researchers quickly conducted four studies in which they compared the effectiveness of T_4 replacement to T_4/T_3 replacement. The ratio of T_4 to T_3 that patients in the studies used was far higher than the 4:1 ratio in Armour and Erfa Thyroid. One aim in the studies was to keep patients' TSH levels within the reference range, which makes the tested T_4/T_3 treatments a form of "replacement."

No difference was found between the two types of replacement therapies. Based on this finding, the endocrinologists who conducted the studies,[23][24][25] others,[26] and endocrinologists who wrote editorials about the studies,[30][43] made a logical error. By using incorrect universal propositions rather than correct singular ones, they sweepingly denounced as no more effective than T_4 replacement each and *all* T_4/T_3 therapies—not just the T_4/T_3 *replacement* tested in the studies.

They did not bother to note that the T_4/T_3 therapy they studied was not the T_4/T_3 therapy long used by clinicians who have reported treatment results superior to those of T_4 replacement. That superior treatment was the use of desiccated thyroid and synthetic T_4/T_3 products with a T_4/T_3 ratio of 4:1 or lower. I first reported this logical error of the endocrinology researchers and editorialists in 2003 and again in 2006.[8] But to this date none of them have responded. I hope that the British Thyroid Association (BTA) will not be similarly silent. (For a detailed description of the endocrinologists' logical error, see my critique of the first four T_4 vs T_4/T_3 studies that followed the 1999 Bunevicius study.[8,pp.2-4])

The Committee made the same error as the researchers who conducted the T_4 replacement vs T_4/T_3 replacement studies and the endocrinologists who wrote editorials about them. I would like to remind the Committee of the words of one of their countrymen who was one of the greatest intellects in history, Lord Bertrand Russell: "I do like clarity and exact thinking, and I believe that very important to mankind. Because, when you allow yourself to think inexactly, your prejudices, your bias, your self interest come in in ways you don't notice, and you do bad things without knowing that you're doing them. Self deception is very easy. So I do think exact thinking immensely important."[5]

Instability of T_4 Products

Eric P. Duffy, PhD is Director, Division of Post-Marketing Evaluation Office of New Drug Quality Assessment, OPS, FDA. In *2006*, he presented a slide presentation titled "Stability Of Levothyroxine Sodium Products."[2] On slide 8, Dr. Duffy wrote: "Levothyroxine Tablet Stability: Levothyroxine sodium (T_4) is labile to [prone to reduced potency by] the following: Heat, moisture, oxidative conditions, chemical reactions. These conditions typically occur during levothyroxine formulation, tableting, packaging, and storage." He then wrote, "*Many* levothyroxine drug products have exhibited: history of sub-optimal stability profile, significant loss of potency over shelf life, [and] inconsistent stability profiles within an individual manufacturer's drug product line." (Italics mine.)

Another FDA scientist, Steven B. Johnson, Pharm.D., is with the Division of Pharmaceutical Evaluation II of the FDA. In a *2003* slide presentation, he said, "Levothyroxine degrades quickly with exposure to light, moisture, oxygen, and carbohydrate excipients."[3,slide 5] He noted that over the years, companies worked to improve the stability of their levothyroxine products, and significant changes occurred.[3,slide 6] Obviously, stability was a problem; why else would companies work to improve stability? In fact, the stability problem has been so substantial that until the FDA stopped the practice, many companies engaged in "stability overage"; that is, the companies would add more than 100% of the T_4 designated on the product label. They did so because they assumed that potency would be lost, and they compensated for the loss by packing extra T_4 into the tablets.[2,slide 9][3,slide 5]

The instability of levothyroxine tablets is noteworthy, especially in view of the Committee's claim that levothyroxine products are more stable than desiccated thyroid products. Dr. Johnson cited the noteworthy FDA recall record of levothyroxine: "Between 1990 and 1997: 10 recalls, 150 lots, and 100 million tablets."[3,slide 5] (Italics mine.) The reasons for the FDA recalls are also noteworthy: "Content uniformity, sub-potency, and stability failures."[3,slide 5]

Whether intentional or not, the BTA's Executive Committee painted a grossly imbalanced picture of the comparative stability of desiccated thyroid and levothyroxine. The Committee clearly cast an unfavorable light on desiccated thyroid by presenting the meager evidence against it, while failing to disclose the copious evidence against T_4. The fact is that the stability of levothyroxine has been far more in question at the FDA than has that of desiccated thyroid.

Stability of Natural Desiccated Thyroid

According to the Committee: "The concentration of thyroid hormones in Armour Thyroid USP is regulated by the manufacturer to United States Food and Drug Administration (FDA) standards. Despite this, *there have been significant problems with the stability of Armour Thyroid in recent years*, prompting a massive recall of tablets." (Italics mine.) The Committee also wrote, "An FDA enforcement removed more than half a million bottles of Armour Thyroid from US pharmacies in 2005 due to unstable concentrations of thyroid hormone in the preparation."[1] Indeed, batches of the product were recalled in 2005.[9] But the Committee mentions "problems with the stability . . . *in recent years*." (Italics mine.) This suggests that the FDA has repeatedly recalled Armour batches in two or more years. But the Committee cites only the 2005 recall; I cannot find documentation for others.

The Committee's purpose in citing the Armour recall appears to have been to implicitly argue that levothyroxine products (levothyroxine sodium, thyroxine, and T_4) are more stable than desiccated thyroid products. If so, the Committee engaged in card-stacking of evidence, as it failed to disclose a highly relevant fact: the T_4 products Synthroid and Levoxyl have been recalled far more often than Armour, Erfa Throid, and other desiccated thyroid hormone products.

Anyone with Internet access can view the public record at www.fda.gov/search.html. Searches show that the many recalls of T_4 products dwarf the few recalls of desiccated thyroid.

Clinicians and patients interested in the relative merits and demerits of T_4 and desiccated thyroid should be aware that desiccated thyroid products are not carelessly produced. The Committee failed to note that manufacturers of desiccated thyroid take proper steps to ensure its potency before the products are shipped to pharmacies. For example, manufacturer of USP Thyroid tablets take appropriate steps to ensure consistent potency from tablet-to-tablet and lot-to-lot. The manufacturer not only performs analytical tests on the raw material (Thyroid USP powder), but also on the tablets (finished products) to measure actual T_4 and T_3 activity.[11] As a result of this attention to quality, only two recalls—voluntary ones—have occurred in the past eight years. These recalls included fewer than one hundred bottles. The recalls were for a labeling problem, *not* for instability or potency variability as with levothyroxine products.

Ineffectiveness of T_4 Replacement for Many Patients

The endocrinology specialty has long claimed that T_4 replacement is effective for most hypothyroid patients, and that patients need no other treatment such as T_4/T_3 therapy. However, as I wrote in a 2006 review (and in 2003) of four T_4 vs T_4/T_3 studies published in 2003, T_4 replacement is ineffective for many hypothyroid patients.[8,p.14] At that time, at least six studies had shown this to be true.[7][15][16][23][24][25][26][27][28] As I said above, in the 1999 Bunevicius study[7] patients who had been on T_4 replacement substituted 12.5 µg of T_3 for 50 µg of their usual T_4 dosages. The neuropsychological function of patients who added T_3 to their treatment improved. It is obvious but worth emphasizing that from the patients' improved neuropsychological function, it follows that their previous T_4 monotherapy had failed to provide them the higher level of function that T_4/T_3 provided.

In a large, community-based questionnaire study in 2002,[27] researchers evaluated the health status of hypothyroid patients using T_4 replacement therapy. Compared to matched control patients, hypothyroid patients on "adequate" dosages of T_4 had a higher reported incidence of four diseases: depression, hypertension, diabetes, and heart disease. Hypothyroid patients on inadequate T_4 replacement (their TSH levels were elevated) also had a higher incidence of strokes. In addition, hypothyroid patients chronically used more prescription drugs, especially for diabetes, cardiovascular disease, and gastrointestinal conditions. Patients on T_4 replacement had scores 21% higher (worse) than controls on the General Health Questionnaire. The researchers wrote, "This community-based study is the first evidence to indicate that patients on thyroxine replacement even with a normal TSH display significant impairment in psychological well-being compared to controls of similar age and sex."[27,p.577]

In the study by Cassio et al.,[26] researchers treated infants who had congenital hypothyroidism with either T_4 or T_4/T_3 replacement therapy. The infants had scores on psychological tests that were lower than those of infants who were not hypothyroid. *The two replacement therapies did not improve the scores of the hypothyroid infants*, so their psychological impairment presumably persisted.

To take part in the Sawka et al. study,[24] patients on T_4 replacement had to have test evidence of depression: that is, they had to have, ". . . evidence of depressive symptoms as defined by a score of more than 5 on the 30-item General Health Questionnaire . . . on 2 occasions, at least 2 wk apart."[24,p.4551] The researchers found that replacement therapies were not effective for the patients and, again, presumably left them depressed.

In the Walsh et al. study,[23] typical symptoms suffered by hypothyroid patients who were dissatisfied with their T_4 replacement included "tiredness, impaired well-being, or weight gain."[23,p.4544] The study showed that replacement therapies were ineffective for these patients and left them suffering from their symptoms.

In addition to the four studies I just mentioned, two other studies also showed the ineffectiveness of T_4 replacement.[15][16] The study by Escobar-Morreale et al.[15] is especially informative. The researchers reported that patients on both T_4 and T_4/T_3 replacement "performed worse than controls in the time score and Visual Scanning Test . . . ."[15,p.420] But patients who used a 5:1 ratio of T_4 and T_3 did not perform worse than the healthy control subjects. Also, patients on T_4 and T_4/T_3 replacement therapies did worse than healthy controls on two other tests (isovolumic relaxation time and brainstem evoked potentials), but patients who used T_4 and T_3 in a 5:1 ratio did *not* do worse than controls.[15,p.420] This positive result for 5:1 T_4/T_3 therapy is evidence from Escobar-Morreale et al. that the therapy was more effective than the two forms of replacement therapy.

False Reporting by the Committee, Escobar-Morreale et al., and Grozinsky-Glasberg et al.

In this rebuttal to the Committee of the BTA, I cite incidences of unbalanced presentation of data that deny readers an accurate understanding of the research concerning the relative stability, safety, and effectiveness of desiccated thyroid as comparted to synthetic T_4 products. In the pursuit of scientific truth, these instances of unbalanced presentation are lamentable. However, the Committee, Escobar-Morreale et al., and Grozinsky-Glasberg et al. gave false reports concerning the research data that are an even more egregious departure from accurate reporting.

The Committee's extrapolation that T_4/T_3 therapies provide no benefits

The Committee of the BTA wrote, "Since this initial study, [the 1999 Bunevicius et al. study[7]] there have been a further [*sic*] seven rigorously conducted ('randomized, double-blind, placebo-controlled') studies . . . . *None of the subsequent studies showed a beneficial effect of combined T_4/T_3 therapy* on measures of wellbeing, health and mental functioning." (Italics mine.)

The Committee then concluded, ". . . combined T_4/T_3 cannot be recommended *because of a lack of benefit* . . . ." The studies of T_4/T_3 therapy the Committee referred to involved synthetic hormones, none of which were used in the 4:1 T_4/T_3 ratio as contained in desiccated thyroid. But in its document, the Committee implies by extrapolation that desiccated thyroid, too, cannot be recommended because of a lack of benefit. This is a clear-cut *non sequitur*.

I request that the Committee reconcile its conclusion, at the very least, with the evidence I cite in this section. This evidence directly contradicts the Committee's conclusion. Older studies show that T_4/T_3 in the form of desiccated thyroid was at least as effective as synthetic T_4. As Cobb and Jackson wrote in a drug therapy review, desiccated thyroid products are equipotent to T_4 alone in treating hypothyroidism.[19,p.53] This was determined by a study of the potency of desiccated thyroid using an antigoitrogenic assay in rats.[13] Most studies of T_4/T_3 therapy have not been of desiccated thyroid itself, although at least 12 studies did directly compare desiccated thyroid to T_4 alone.[4][29][31][32][33][35][37][38][39][40][42][45] The Committee, however, did not cite these studies; instead, it extrapolated to desiccated thyroid from studies that compared synthetic T_4 to synthetic T_4/T_3 combinations. Reading the same studies the Committee referred to makes clear that its claim of a lack of benefit of desiccated thyroid is false.

First Bunevicius study. In a study published in 1999, Bunevicius et al.[7] included 26 hypothyroid women. Eleven had autoimmune thyroiditis and 15 had been treated for thyroid cancer. Patients either continued their usual dose of T_4, or they substituted 12.5 µg of T_3 for 50 µg of their usual dosage of T_4.

Bunevicius et al. later wrote that when patients were undergoing T_4/T_3 therapy, they had "clear improvements in both cognition and mood, the latter changes being greater." [21,p.167] The researchers also wrote, "The patients who had been treated for thyroid cancer showed more mental improvement than the women with autoimmune thyroiditis . . . ."[21,p.167] However, *patients in both groups improved on some measures*.[21,pp.169-171]

This is important to note because in the review paper that the Committee cited, Escobar-Morreale et al. falsely reported that *only* thyroid cancer patients improved. Specifically, they wrote, ". . . the presumed benefits of T_3 substitution were restricted to athyreotic thyroid cancer patients . . . ."[17,p.4949] Consider, however, what Bunevicius and Prange actually reported: Referring to visual analog scales, they wrote, "The advantages [improvements] for combined treatment were statistically significant in the . . . [autoimmune thyroiditis] group on 4 scales, in the . . . [thyroid cancer] group on 6 scales."[21,p.170] Table 5 in Bunevicius and Prange's report shows this to be true.[21,p.172] Escobar-Morreale et al., then, are guilty of false reporting.

Second Bunevicius study. In the second Bunevicius study,[22] patients were hypothyroid from thyroidectomy for Graves' disease. The patients substituted 10 µg of T_3 for 50 µg of their usual T_4 monotherapy dose. In their first study, Bunevicius et al. substituted 12.5 µg of T_3 for 50 µg of T_4.[7] Despite the more modest substitution dose of 10 µg of T_3 in the second study, the results indicated that patients improved with T_4/T_3 therapy.

Compared to baseline scores when patients were using T_4 replacement, the patients had statistically significant improvement on three measures.[22,p.130] Allowing for a slightly larger significance level (p = 0.06), the patients using T_4 also improved on one other measure—a total of four measures. Similarly, when patients used T_4 and T_3, they significantly improved on three measures. But allowing for slightly larger significance levels ($p = 0.06$ to 0.08), these patients also improved on four more measures—a total of seven measures. This means that with T_4 alone, patients improved on four measures, while on T_4/T_3, they improved on seven. With the slightly expanded significance levels, then, patients improved more with T_4 and T_3 combined than they did on T_4 alone.

Bunevicius et al. wrote: "Thus, to a statistically significant degree, the substitution of 10 µg of T_3 reduced the concentration of free T_4, as well as the symptoms of hypothyroidism and subjective tension, while improving pairs recalled on the Digit Symbol Test. In addition, it tended to reduce the symptoms of hyperthyroidism, to improve mood on the Beck Depression Inventory, as well as feelings of confusion on the Visual Analog Scale, and to improve the raw score on the Digit Symbol Test and forward recall on the Digit Span Test."[22,pp.131-132]

In the 2005 Saravanan study,[14] patients substituted 10 µg of T_3 for 50 µg of their T_4 dosages. The researchers wrote that patients on the different therapies had no differences in a number of test scores. However, patients who used T_4/T_3 had some improvements compared to patients who used T_4 alone. The researchers reported, ". . . a *significantly greater reduction in psychiatric caseness* [patients who met the criteria for different disorders] was seen in the T_3 group compared with T_4 alone . . . . *Improvement was also seen* in the HADS anxiety score [the Hospital Anxiety and Depression questionnaire] at 3 months."[14,p.807] (Italics mine.)

Patients' preference for T_4/T_3 therapy. The Committee wrote that in *two* studies in which researchers compared T_4 to T_4/T_3 therapy, patients preferred T_4/T_3 therapy. This is a factual error by the Committee. Actually, patients preferred or were more satisfied with T_4/T_3 therapy in *five* studies.[7][15][16][22][36]

In each of the five studies, far more patients preferred T_4/T_3 therapy over T_4 replacement. Combining the preference data from the five studies, of 236 patients, 110 patients had no preference. Only 27 patients preferred T_4 replacement while 99 preferred some form of T_4/T_3 therapy. (See Figure 3.)

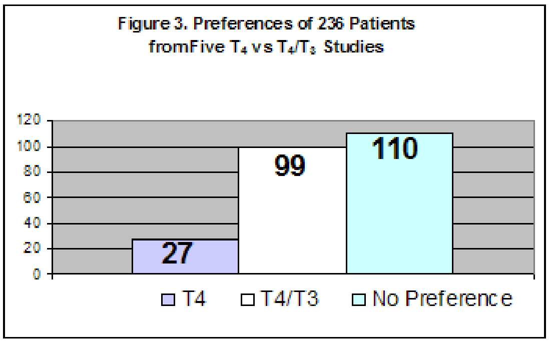


Figure 3. Preferences of 236 Patients from Five T_4 vs T_4/T_3 Studies

In two studies,[15][16] patients used T_4/T_3 in a ratio of both 10:1 and 5:1. Of the 61 patients involved, 31 preferred the 10:1 ratio; 30 preferred the 5:1 ratio.

One of the five studies was published in 1999,[7] another in 2002,[22] and three other studies were published in 2005[15][16][36]—all well before the 2007 Committee document published by the British Thyroid Association.[1] Despite this, the Committee failed to mention that patients preferred T_4/T_3 therapies. Perhaps this neglect of the Committee was due to its dependence on the reviews by Escobar-Morreale et al.[17] and Grozinsky-Glasberg et al.[18] rather than the original study reports the reviewers purportedly analyzed. In any case, neglecting this important finding constitutes an unbalanced presentation of data that favors T_4 replacement over T_4/T_3 therapies.

The 1999 and 2002 studies that the Committee did not reference were the first and second Bunevicius et al. studies.[7][22] At the end of the 1999 study, the researchers asked patients about their preferences for a particular form of treatment. The researchers wrote, "When asked at the end of the study whether they preferred the first or second treatment, 20 patients preferred thyroxine plus triiodothyronine, 11 had no preference, and 2 preferred thyroxine alone ($p = 0.001$)."[7,p.427] (See Figure 4.)

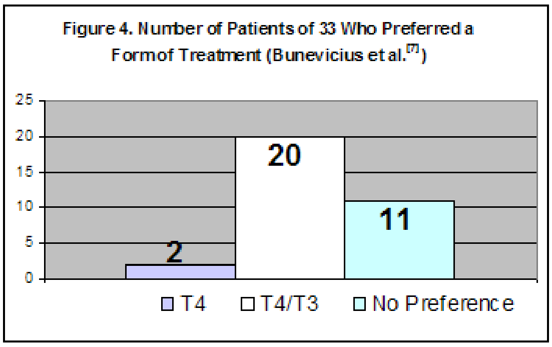


Figure 4. Number of Patients of 33 Who Preferred a Form of Treatment (Bunevicius et al.[7])

At the end of the 2002 study, the researchers asked patients about their preferences. "Six patients," they wrote, "preferred combined treatment, reporting increased energy, better performance, and decreased 'tension in the eyes.' Two preferred monotherapy with T_4, and two found no difference."[22,p.132] (See Figure 5.)

In the Applehof et al. study, patients who used T_4/T_3 therapy were more satisfied with the treatment. In fact, the researchers found a linear relationship between the use of T_3 and the number of patients preferring treatment: In the T_4 monotherapy group, only 29.2% were satisfied with the treatment; in the group who used T_4/T_3 therapy in a 10:1 ratio, 41.3% were satisfied; and in the group that used T_4/T_3 therapy in a 5:1 ratio, 52.2% were satisfied. (See Figure 1.)

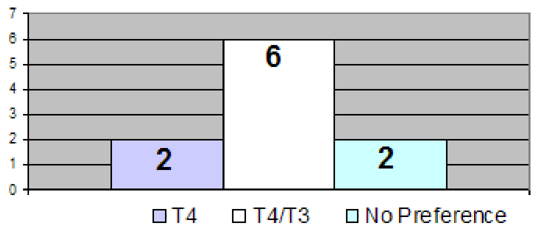


Figure 5. Number of Patients of 10 Who Preferred a Form of Treatment (Bunevicius et.[22])

Escobar-Morreale et al.[15] and Rodriquez et al.[36] also reported more satisfaction with T_4/T_3 therapies (see Figures 2 and 6). Unfortunately, Grozinsky-Glasberg et al., for all practical purposes, gave no attention to patients' preference for T_4/T_3 therapies. To their credit, Escobar-Morreale et al. did mention patients' preference for T_4/T_3 in their abstract, the body of their review, and in their conclusion section.[15]

In some studies, researchers did not inquire about patients' satisfaction with tested therapies. In the Walsh et al.[23] study the researchers did inquire, and there was no difference in patients' preferences.

The Committee's parroting of false statements by Escobar-Morreale et al. and Grozinsky-Glasberg et al.

The Committee wrote, "There is no evidence to favour the prescription of Armour Thyroid in the treatment of hypothyroidism over the prescription of thyroxine sodium."[1] The Committee appears to have argued against desiccated thyroid by appropriately including it among T_4/T_3 therapies. Its claim of no benefit of these therapies over T_4 replacement, however, is false. It is possible that the source of the Committee's erroneous conclusions are false statements by Escobar-Morreale et al. and Grozinsky-Glasberg et al. in their reviews of the studies testing T_4 alone vs T_4/T_3 therapies.

As Figures 1 through 6 show, patients' satisfaction is a benefit often provided by T_4/T_3 therapies. In their meta-analysis of the T_4 vs T_4/T_3 studies, Grozinsky-Glasberg et al. side-stepped this important finding. They merely included the term "satisfaction" in a table,[16,p.2594] and they briefly mentioned patients dissatisfied with T_4 replacement.[16,p.2597] They did not include the words "prefer" or "preferred" in their paper, and they did not include the data from the five studies in which patients by far preferred T_4/T_3 therapies.

Keep in mind that Applehof et al. reported that weight loss with T_4/T_3 therapy correlated with patients' satisfaction with the treatment.[16,p.2672] But Grozinsky-Glasberg et al. were so dismissive of weight loss from T_4/T_3 therapy that they contradicted themselves on different pages of their report: In their results section under "Weight Changes" they wrote, "The weight in the combination group was lower at the end of the study, and *this difference reached statistical significance* . . . ."[18,p.2596] (Italics mine.) Yet in their abstract they wrote, "No difference was found in . . . body weight . . . ."[18,p.2592] And in their discussion section, they wrote ". . . there was no significant difference in terms of weight change."[18,p.2597]

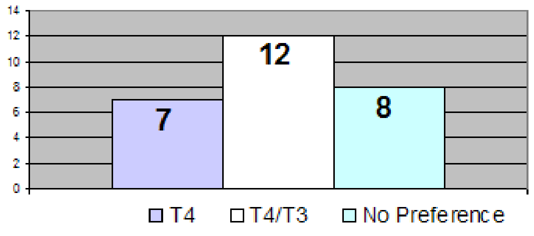


Figure 6. Number of Patients of 27 Who Preferred Each Form of Treatment (Rodriquez et al.[48])

Grozinsky-Glasberg et al. also falsely reported the outcome of Bunevicius and Prange's reanalysis of their data from their 1999 study.[21] Grozinsky-Glasberg et al. wrote: "Only one trial found significant benefit of combination therapy over the monotherapy. *It was later suggested that this benefit was associated with the cause of hypothyroidism and that only athyreotic [without a thyroid gland or endogenously produced thyroid hormone] thyroid cancer patients benefited from the combination therapy, whereas patients with autoimmune thyroiditis did not.*"[18,p.2597] (Italics mine.) Yet *clearly*, Bunevicius and Prange's report of their reanalysis shows this statement to be patently false. In Table 5 of Bunevicius and Prange's report, they showed improvement on visual analog scales among thyroiditis patients. Compared to the patients' baseline measures (when they were on T_4 replacement), testing when they were using T_4/T_3 therapy revealed *statistically significant (p = 0.02)* reductions in sadness, confusion, fearfulness, and irritability.[21,p.172]

In their report, Bunevicius and Prange wrote, "Table 5 shows results on the visual analogue scales. *For each diagnostic group* [thyroid cancer *and* autoimmune thyroiditis patients] on all 8 scales, there was at least a *tendency for improvement after* T_4 *plus* T_3 *compared to* T_4 *alone*."[21,p.170] They then wrote, "The advantages for *combined treatment were statistically* *significant in the AT [autoimmune thyroiditis] group* on 4 scales, in the TC [thyroid cancer] group on 6 scales." (All italics mine.) These statements by Bunevicius and Prange and Table 5 in their report show that in their meta-analysis paper, Grozinsky-Glasberg et al. falsely reported the results of the Bunevicius and Prange reanalysis.

Maybe the mistake of Grozinsky-Glasberg et al. was in taking at face value what Escobar-Morreale et al. stated in a review of T_4 vs T_4/T_3 studies. (Grozinsky-Glasberg et al. cited the review paper at the end of their false statement about the result of the Bunevicius and Prange reanalysis.[18,p.2597]) Escobar-Morreale et al. wrote, "*A subsequent reanalysis of the data*, removing from the initial study the data from the two men, from four depressed women, and from a woman who presented with increased serum TSH levels at baseline, *revealed that the findings originally reported were maintained only in the subset of athyreotic patients and not in women with autoimmune thyroiditis*."[17,p.4949] (Italics mine.) Thus, Escobar-Morreale et al. may be the source of false statements about Bunevicius and Prange's finding. Unfortunately, other researchers have reiterated the false statements.[36]

Eleven Studies Have Compared T_4-Replacement to Natural Desiccated Thyroid: Factual Error of the Committee

Referring to T_4 and desiccated thyroid, the Committee wrote, "*There has never been a direct comparison of these two treatments.*" (Italics mine.) When I read this, I immediately turned in my desk chair and pulled from a filing cabinet 12 published reports of "direct comparison" of these two forms of treatment.[4][29][31][32][33][35][37][38][39][40][42][45] Researchers reported using Armour *per se* in three of the studies.[4][39][40]

One study was published in 1972.[39] The researchers wrote, "The present study was designed to compare the effects of desiccated thyroid and monosodium l-thyroxine [T_4], administered by mouth, on serum lipids in a group of hypothyroid patients." The researchers reported, ". . . a cholesterol-lowering effect was manifested by the time of first testing after institution of desiccated thyroid or l-thyroxine treatment." They wrote further, "The magnitude of the hypolipidemic [fat lowering] effects were [*sic*] similar when desiccated thyroid and l-thyroxine were give [*sic*] orally in therapeutic [*sic*] equivalent doses."[39,p.1047]

Another "direct comparison" was published in 1978.[40] The researchers wrote, "The biologic effect of the two therapies was compared by estimating by interpolation the dose of thyroid hormone that caused the peak serum TSH after TRH to fall to 5 μU/ml."[40,p.1518] They concluded, ". . . a daily dose of 100 mcg of T_4 was on average equal in biologic activity to 101 mg of desiccated thyroid; 60 mg of desiccated thyroid was equal to 60 mcg of T_4."[40,p.1518]

Two other research groups showed that the 60 mg of desiccated thyroid had the effect of 100 μg of T_4 in raising the basal metabolic rate.[29][42] A number of other researchers have made "direct comparison" of desiccated thyroid and T_4.[4][31][32][33][34][37][38] These studies show that the Committee's statement that Armour (and by extension, similar desiccated thyroid products) has not been directly compared to T_4 was an *ex cathedra* pronouncement, one that is clearly false.

Necessity of retractions. In the interest of precision and accuracy in the science of thyroidology—in fact, in the interest of its credibility—Escobar-Morreale et al., Grozinsky-Glasberg et al., and the Executive Committee of the BTA are compelled to correct their false reports of Bunevicius and Prange's actual study results. Also, the Committee is compelled to correct its false statement that no studies have compared T_4 to desiccated thyroid.

As the statements of these groups of authors stand, they drive the body of scientific information in clinical thyroidology away from the goal of accuracy and truth. Regarding Escobar-Morreale et al. and Grozinsky-Glasberg et al., we have to look no further than the Committee's document to confirm that their incorrect and inexact reports send ripples of falsehood through the sea of beliefs within the field of clinical thyroidology and of its decision-makers. Setting off such ripples is contrary to the traditional aims of science and is not a worthy legacy of these authors. On the grounds of science ethics, they are obligated to rectify their errors.

Harmful Ineffectiveness of T_4 Therapy

It appears that when the Committee was writing its document, it had the impression that research had unequivocally established the safety and effectiveness of T_4 replacement. The Committee wrote, "The BTA committee [*sic*] cannot recommend a treatment with possible side-effects [*sic*], [such as desiccated thyroid], *when a safe and equally-well established treatment [T_4 replacement] exists*."[1] (Italics mine.) The proposition that T_4 replacement is safe and effective for all patients, however, is simply false. Studies show that for many people, the therapy is harmful by virtue of its ineffectiveness.

In 2000, Bunevicius and Prange wrote: "It is conventional to provide replacement treatment with T_4 alone, in the belief that each tissue will make sufficient quantities of T_3 (the more potent hormone) for its own needs. Nevertheless, *it has long been noted that after* *treatment with T_4 alone not all patients are entirely well.*"[21,p.167] (Italics mine.) Here they reference a report by Taylor et al.[44] *published in 1970.* Today, 39 years later, studies are still showing that T_4 replacement is ineffective for many patients, subjecting them to the ravages of deficient thyroid hormone regulation of cell function. This is indicated by patients who were "stable" on T_4 replacement: (1) still suffering from hypothyroid symptoms and having various abnormal test scores,[23][24][26][27] (2) entering a study hoping they would feel better on another thyroid hormone therapy,[25] (3) having disorders plausibly explained by too little thyroid hormone regulation,[10][16][27][36] (4) gaining and not being able to lose weight,[12][20] and (5) suffering potentially-fatal diseases associated with untreated or undertreated hypothyroidism and using more medications for those diseases.[27]

Inadequate regulation of cell function by thyroid hormone in patients using T_4 replacement can cause them to not only suffer, but to potentially die earlier than otherwise. It can also greatly increase medical and societal costs. Because of these harmful effects, it is reasonable to conclude that T_4 replacement—in which the TSH is kept within the reference range—is injurious to many hypothyroid patients and to society at large.

Adverse effects in studies of T_4 and T_4/T_3 therapies. The Committee wrote in its document, "Three of the seven studies show harmful or undesirable effects of the T_4/T_3 combination."[1] One might assume from the Committee's statement that desiccated thyroid and other T_4/T_3 therapies are likely to cause adverse effects. But it would have been obvious that this is not true had the Committee accurately reported what was found in the three studies.[15][16][22]

In one of the studies, Escobar-Morreale et al. compared T_4 and T_4/T_3 replacement to T_4/T_3 therapy in a 5:1 ratio. After the study ended they wrote, "No adverse effects were reported with any of the treatments."[15,p.420] They also reported the proportion of patients who had increased heart rates. They defined increased rates as higher than 120 beats/min in daytime and higher than 100 beats/min at night. Of 420 patients on T_4 replacement, 13 had raised heart rates. Of 376 patients using T_4/T_3 replacement, 13 had increased rates. But of 377 patients using T_4/T_3 therapy in a 5:1 ratio, only 7 had increased heart rates.[15,p.420] The researchers reported, however, that the groups did not differ statistically.

In the study by Appelhof et al.,[16] patients who used T_4/T_3 therapy in a 5:1 ratio had no adverse effects. In contrast, patients who used T_4 and T_4/T_3 replacement did have adverse effects. Appelhof et al. wrote of adverse effects in the study: "One participant (5:1 [T_4/T_3] group) withdrew because of unexpected travel abroad for family matters and was excluded from all analyses. Seven patients withdrew because of side effects, four in the LT_4 group and three in the 10:1 [T_4/T_3] group. Various side effects were mentioned (e.g. fatigue, muscle aches, dizziness, irritability), but no specific complaints could be identified for those on combination therapy."[16,p.2668] (see Figure 7).

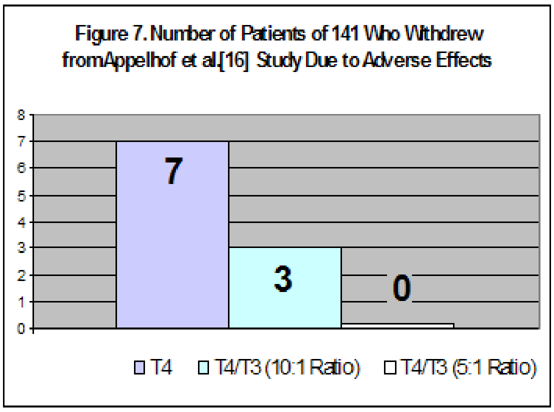


Figure 7. Number of Patients of 141 Who Withdrew from Appelhof et al[16] Study Due to Adverse Effects

In the second Bunevicius et al study,[22] the researchers compared T_4 to T_4/T_3 replacement. More patients were satisfied with T_4/T_3 than with T_4 replacement. (Figure 5) Perhaps the lack of satisfaction of patients using T_4 replacement resulted from the adverse effects they experienced: two patients reported that they experienced "sensitiveness of the heart," and one reported "hand tremor."[22,p.132]

Of most relevance to desiccated thyroid, studies of patients who used T_4/T_3 therapy in a ratio close to that of desiccated thyroid had no adverse effects. The Committee failed to report this, just as it failed to report that patients in studies of T_4 replacement have had adverse effects. By failing to report accurately, the Committee cast an unjustified shadow of doubt over T_4/T_3 therapies, including desiccated thyroid, and it flooded T_4 replacement with an indefensible light of safety.

Conclusions

In its document on desiccated thyroid and T_4/T_3 therapies, the Executive Committee of the British Thyroid Association presented a grossly unbalanced picture of the stability of levothyroxine sodium, Armour Thyroid, and by extension, other prescription desiccated thyroid products such as Erfa Throid. The Committee also reiterated false statements about T_4/T_3 therapies contained in reports by other researchers. Furthermore, the Committee did this without mentioning or accounting for the other researchers' variances from the facts.

In addition, in its denouncement of desiccated thyroid, the Committee failed to account for the outcome of two highly relevant studies.[15][16] In these studies, treatment with T_4 and T_3 in a 5:1 ratio (close to the 4:1 ratio in desiccated thyroid) was more effective in some ways than was T_4 replacement and T_4/T_3 replacement.

While warning of adverse effects from desiccated thyroid, the Committee failed to disclose the complete lack of adverse effects among patients who used T_4 and T_3 in a 5:1 ratio.[15][16] It also failed to disclose that patients using T_4 replacement and T_4/T_3 replacement (in 10:1 to 15:1 ratios) had adverse effects.[16]

Moreover, the Committee failed to account for three harmful effects from T_4 replacement. These are: (1) continued suffering from hypothyroid symptoms by patients who are restricted to T_4 replacement therapy[7][15][16][23][24][25][26][27][28]—in as high a percentage as 50%,[27] (2) a higher incidence in these patients of diseases associated with hypothyroidism,[27] and (3) the use of more drugs by the patients.[27]

At the top of its homepage, the BTA once indicated that it is "Encouraging the Highest Sandards [*sic*] of Research and Patient Care." I trust that the BTA's integrity is such that it will conduct itself in accord with this statement. Hence, I also expect that its Executive Committee will revise its document on desiccated thyroid based on a careful reading of the *original* reports of the studies to which they refer, taking note of the findings I have described. As the Committee does so, the scientific and humanitarian imperatives are that it abide by the advice of one of the United Kingdom's—indeed, history's—most eminent logicians: "When you are studying any matter or considering any philosophy, ask yourself *only* 'what are the facts, and what is the truth that the facts bear out.' Never let yourself be diverted either by what you wish to believe, or by what you think would have beneficent social effects if it were believed. But look *only* and *surely* at *what are the facts*."[6]

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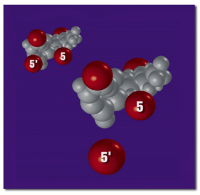

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| General Letters | Dr. Allahabadia's Reply |

Subject: Reply to rebuttal to the BTA's opinions
From: editor@thyroidscience.com
Date: Mon, March 15, 2010 9:01 am
To: Amit.Allahabadia@sth.nhs.uk
Secretary, British Thyroid Association

Dear Dr. Allahabadia,

I initially wrote to you in March 16, 2009—one year ago—asking that the British Thyroid Association (BTA) respond to my rebuttal <http://www.thyroidscience.com/Criticism/lowe.3.16.09/bta.rebuttal.htm> to its opinions on levothyroxine, T4/T3 combination therapy, and desiccated thyroid. You wrote back to me in August 2009 saying that the BTA would respond “in due course.”

I consider that due course has long since passed. If the BTA does not enter discourse over its opinions, then its opinions can justifiably be considered authoritative and dogmatic rather than rational and scientifically-based.

I request once more that the BTA reply to the various points in my rebuttal. Considering how long it has been since I initially wrote to the BTA, a prompt response from the BTA is imperative. The reason is that many practitioners are likely to accept without question that the BTA’s opinions are scientifically accurate. Because some of the BTA’s opinions, expressed in its Executive Committee’s document, are patently false, which

I documented in my rebuttal, some of these practitioners may make decisions on behalf of hypothyroid patients that adversely affect the health and well-fare of hypothyroid patients.

It is in the interest of quality care for hypothyroid patients, and in the spirit of traditional scientific values, that I ask again that the BTA to reply to my rebuttal.

Sincerely,
Dr. John C. Lowe
Editor-in-Chief
Thyroid Science

Subject: RE: Request for reply from the British Thyroid Association
From: Amit.Allahabadia@sth.nhs.uk
Date: Tue, April 7, 2009 4:22 am
To: editor@thyroidscience.com

Dear Dr Lowe

Thank you for e-mail. The Executive Committee of the British Thyroid Association will consider your comments in due course in consultation with The Royal College of Physicians.

Best wishes
Dr Amit Allahabadia
Secretary of The British Thyroid Association

Subject: Request for reply from the British Thyroid Association
From: editor@thyroidscience.com
Date: Tue, April 7, 2009 4:11 am
To: Amit.Allahabadia@sth.nhs.uk

To: Dr Amit Allahabadia
Secretary: British Thyroid Association
Sheffield Teaching Hospitals, Sheffield

Dear Dr. Allahabadia,

Below is an email I send to you and the British Thyroid Association (BTA) on March 16, 2009. In the email, I invited a response from the BTA to be published without censorship at *Thyroid Science* in the spirit of scientific discourse. I have not received a response from you or from any other representative of the BTA. I will be grateful if you or another representative will give us the courtesy of letting us know, at minimum, that you received my email, but hopefully also letting us know whether we can expect a response from the BTA. Thank you for taking the time to reply.

For your convenience, below is the webpage address to my rebuttal to the BTA's document on natural desiccated thyroid and synthetic T4/T3 therapies:

http://www.thyroidscience.com/Criticism/lowe.3.16.09/bta.rebuttal.htm

Best regards,
Dr. John C. Lowe
Board Certified: American Academy of Pain Management
Director of Research: Fibromyalgia Research Foundation
Editor-in-Chief: ThyroidScience.com
(603) 391-6061, www.drlowe.com

drlowe@drlowe.com Tammy@drlowe.com
drlowe@FibromyalgiaResearch.org

Subject: Rebuttal to British Thyroid Association's document on natural desiccated thyroid
From: editor@thyroidscience.com
Date: Mon, March 16, 2009 2:12 pm
To: Amit.Allahabadia@sth.nhs.uk

To: Dr Amit Allahabadia
Secretary: British Thyroid Association
Sheffield Teaching Hospitals, Sheffield

Dear Dr. Allahabadia,

I have included below a link to a rebuttal I have written to the British Thyroid Association (BTA). The rebuttal concerns the BTA Executive Committee's 2007 document on natural desiccated thyroid and levothyroxine. After having critically analyzed the Committee's document, I believe it constitutes a gross disservice to patients and clinicians who might read and be mislead by its unbalanced presentation of evidence and the false statements it contains. I feel it is proper to let the BTA know about my rebuttal so that its officials can respond, hopefully by correcting the misinformation the 2007 document contains. We at *Thyroid Science*, of course, will be happy to publish any statement the BTA decide to make in response to the rebuttal.

http://www.thyroidscience.com/Criticism/lowe.3.16.09/bta.rebuttal.htm

All best wishes,

Sincerely,
Dr. John C. Lowe
Board Certified: American Academy of Pain Management
Director of Research: Fibromyalgia Research Foundation
Editor-in-Chief: ThyroidScience.com
(603) 391-6061, www.drlowe.com
drlowe@drlowe.com Tammy@drlowe.com
drlowe@FibromyalgiaResearch.org

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Addenda to:
Dr. Richard Guttler and the "Real Thyroid Experts": Their False and Potentially Harmful Beliefs

by Dr. John C. Lowe
Diplomate: American Academy of Pain Management
Director of Research: Fibromyalgia Research Foundation

1007 Pearl St., Suite 280 Boulder, CO 80032 USA
drlowe@drlowe.com | www.drlowe.com | 303-413-6003

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Addendum 1
Fibromyalgia

We can't doubt what Dr. Guttler believes about the relationship of fibromyalgia symptoms to thyroid disease; he's hurled judgment down to us in the style of a sovereign's edict: About fibromyalgia, he wrote, "There is no relationship between that entity and Hypothyroidism. End of story."[7] (Italics mine.)

Dr. Guttler issued this authoritarian decree without even attempting to refute a substantial body of research—one that shows the main underlying causes of fibromyalgia symptoms to be hypothyroidism and peripheral thyroid hormone resistance. I summarize below what's contained in that body of research.

Many researchers have noted that fibromyalgia symptoms are virtually identical to those of hypothyroidism.[56][57][58][59][60][61][62][63][64][65][66][67][68] Indeed, as my collaborator Jackie Yellin, has shown, the most well-documented features of fibromyalgia are exactly the same as features of hypothyroidism (see Table 1).

Studies by several research teams indicate that 90% of fibromyalgia patients have underlying thyroid diseases.[69][70] Studies by researchers in the U.S., France, Germany, and Italy show that these thyroid diseases include primary and central hypothyroidism and peripheral cellular resistance to thyroid hormone.[57][71][73][74][75][76][78] It's important to note, however, that most patients' fibromyalgia symptoms caused by thyroid disease are compounded by other metabolism-impeding factors. The most common factors are poor diet, nutritional deficiencies, poor physical fitness, and metabolism-impairing drugs.[25]

When fibromyalgia patients receive effective treatment for hypothyroidism or peripheral thyroid hormone resistance, most are fully and lastingly freed from their fibromyalgia symptoms. Several open but systematic trials and several blinded studies have shown that metabolic treatment including thyroid hormone therapy completely relieves most patients' symptoms.[16][72][77][79][80][81][82][83] In another double-blind crossover study, researchers reported a positive therapeutic effect on fibromyalgia from transdermal T3.[14] In a randomized double-blind, placebo-controlled study, clinicians used multiple therapies.[13] In that study, as Peter Warmingham noted in an article titled "Fibromyalgia has been solved,"[12] 90% of the fibromyalgia patients used thyroid hormone and 90% improved. These are the only studies in which patients have largely or fully recovered from fibromyalgia symptoms; each involved thyroid hormone therapies other than T4-replacement, an approach documented to fail to relieve a large percentage of hypothyroid patients of their symptoms.

Table 1. Some symptoms and objectively verified abnormalities in both hypothyroidism and fibromyalgia.*

Reduced slow-wave sleep
Irritable bowel syndrome
Reduced HPA axis function
Urinary frequency
Increased pain perception
Increased substance P
Depression
Cognitive dysfunction
Slow muscle relaxation time
Exercise intolerance
Impaired glycolysis
Increased hyaluronic acid
Reduced brain blood flow
Chronic widespread pain
Increased alpha2-adrenergic receptors on platelets
Dysmenorrhea
Reduced serotonin secretion (platelets)
Joint hypermobility
Reduced growth hormone & somatomedin C
Stiffness & swelling
Sicca symptoms
Orthostatic hypotension
Cold intolerance
Paresthesia
Increased mast cells
Anxiety
Fatigue

*From Jackie Yellin's seminar, Hampshire Hills Sports and Fitness Club, Milford, New Hampshire, Sept. 20, 2001.

If Dr. Guttler doubts the relationship between fibromyalgia symptoms and too little thyroid hormone regulation, he should read three studies by our research team at the Fibromyalgia Research Foundation.[81][82][83] These were double-blind, placebo-controlled, crossover studies. In them, we tested the effects of T3 and placebos on fibromyalgia symptoms. We repeatedly turned the patients' symptoms off and on by switching them from T3 to placebos, much like turning the flow of water off and on by switching a faucet handle one way and then the other.

We conducted another study that showed that thyroid hormone's effectiveness at relieving fibromyalgia symptoms isn't a placebo effect.[15] This study was the first to show long-term effectiveness of a fibromyalgia treatment. The study was a 1-to-5-year follow-up comparing untreated patients to patients treated with metabolic therapy including thyroid hormone. We matched 20 fibromyalgia patients who hadn't undergone treatment with 20 fibromyalgia patients who had. We matched them by sex, thyroid status, and the time since their first evaluation.

We first evaluated all the patients 1-to-5 years before the follow-up study began. We compared those baseline measures with the follow-up measures for each group. Treated patients had improved on all measures of fibromyalgia, and they had decreased their drug use. Untreated patients didn't improve at all, and they were using more drugs. The fact that treated fibromyalgia patients maintained their improvement 1-to-5 years compared to matched untreated patients compels us to formulate a conclusion: Relieving inadequate thyroid hormone regulation produces long-term recovery from fibromyalgia symptoms. That the recovery is not due to a placebo effect is evident from patients' improvement lasting from 1-to-5 years---a span of time that outlast that of documented placebo effects.

In addition to these studies, a huge body of evidence points to too little thyroid hormone regulation as the main underlying cause of fibromyalgia. For example, compared to other people, the fibromyalgia patient has an extremely high level of substance P in his/her spinal cord.[84] Substance P is a chemical that amplifies perception of pain.[85][86][87][88] It amplifies pain perception so much that the patient perceives as painful something that ordinarily is not, such as the pressure of a mattress on his/her back and buttocks.

Thyroid hormone inhibits the production of substance P in the spinal cord.[89][90] When researchers make animals hypothyroid, substance P production is no longer inhibited. The level of substance P then rises steeply in the animals' spinal cords. The high level magnifies the animals' perception of pain, and like fibromyalgia patients, the animals perceive as painful something that ordinarily is not,[85][86] such as a light squeeze of a rat's tail. In humans, the increased pain perception is experienced as chronic widespread aches and pains.[91] Such aches, pains, and tenderness, of course, are the main symptoms fibromyalgia.

In our three blinded studies I mention above,[81][82][83] fibromyalgia patients' pain dramatically decreased or stopped altogether when they took T3. In placebo phases, their pain returned. We assume that the thyroid hormone reduced or stopped our patients' pain by lowering their substance P levels, just as thyroid hormone lowers the substance P level in the cerebrospinal fluid of hypothyroid rats.

Anyone who understands the molecular biology of thyroid hormone regulation knows that the hormone exerts its metabolic effects largely in two ways: by (1) decreasing the density of alpha2-adrenergic receptors on cell membranes, and (2) increasing the density of beta-adrenergic receptors. These two changes accelerate metabolism.

Studies indicate that fibromyalgia patients have the opposite ratio of receptors: (1) an increased density of alpha2-drenergic receptors,[6][????] and, highly likely, (2) a decreased density of beta-adrenergic receptors.[4] These changes slow the patients' metabolism. When researchers treated fibromyalgia patients with a drug (salbutamol) that stimulates beta-adrenergic receptors, their symptoms markedly improved.[4] This evidence points directly to too little thyroid hormone regulation as the main underlying mechanism of fibromyalgia.

I could continue citing such evidence for hundreds of pages. I've already done that, however, in a 1260-page book titled *The Metabolic Treatment of Fibromyalgia*. I cited thousands of studies in the book that point directly to inadequate thyroid hormone regulation as the main underlying cause of fibromyalgia symptoms.[25] Anyone, including Dr. Guttler, who, with a pretense of reaching a scientific conclusion, states that inadequate thyroid hormone regulation is not the cause of fibromyalgia—and while doing so, fails to address the evidence I presented in that book and in many other publications—is making an pseudoscientific statement. There person's statement is thus irrational. I here invite Dr. Guttler to defend his statement about hypothyroid and fibromyalgia against that it is pseudoscientific and irrational. At the same time, I also invite any fibromyalgia researcher to argue the case that inadequate thyroid hormone regulation is not the cause of fibromyalgia. In the past, fibromyalgia researchers, especially rheumatologists, have militated against the the hypothesis by ignoring it. They can no longer do so. If none of them can effective argue the case against this hypothesis, then they must concede by default that it is true.

Many clinicians and researchers have hypothesized causes of fibromyalgia that differ from the inadequate thyroid hormone regulation hypothesis. With rare exception, these theorists have not, within their hypotheses, accounted for or refuted the massive body of evidence supporting the inadequate thyroid hormone regulation hypothesis; as I just stated, they've simply ignored that evidence. Consequently, they've violated the first rule of scholarship in formulating their competitive hypotheses. That rule is to know and account for all credible knowledge within the field of study. By violating this rule, they've sabotaged their own efforts;

their views of fibromyalgia are largely irrelevant to the field and have little if any credibility.

Foremost among these irrelevant and incredible views of fibromyalgia is Dr. Guttler's, expressed as a dictator's decree—"*There is no relationship between that entity* [fibromyalgia] *and Hypothyroidism*. *End of story.*"[7] (Italics mine.)

Return to Critique

Addendum 2

Blind Faith That Laboratory Thyroid Tests Are Infallible

I've extensively studied the scientific literature on thyroid function testing and consulted with many laboratory medicine specialists who are the ultimate experts on the tests. I've also written comprehensively on the merits and demerits of the tests.[25] And I've undoubtedly ordered and interpreted them for as many patients as Dr. Guttler has. Based on that cumulative experience, I'm convinced that reliably accurate clinical decisions cannot be made solely on the basis of thyroid function test results. I consider clinical decisions of doctors who rely exclusively on the tests to be dubious at best and harmful to many patients at worst.

Dr. Guttler argues that his beliefs about the T4 and TSH tests are scientifically-based. For example, he wrote to Mary Shomon, "Your motto should be We're patients.... not lab values, we want our doctors to ignore 50 years of research, and treat us like they did in the 1940's, when therapy was based on symptoms, not facts."[3] Although he suggests that science is the basis of his beliefs, his dogmatic assertions implying that thyroid function tests are infallible are more like evangelism.

In general, the endocrinology specialty shares Dr. Guttler's dogmatic belief in the infallibility of thyroid function tests. Because of this, I'm fond of collecting published studies in which researchers have documented significant, normal variations in the blood levels of TSH, T4, and T3. In my forthcoming book, *Tyranny of the TSH*, I include the most representative of these studies. Here, however, I'll mention only a few to illustrate, contrary to Dr. Guttler's pronouncements, what science *really* shows.

In 1997, researchers reported that when they measured patients' TSH levels week-to-week, the levels did not significantly correlate. The correlation is reported as an "r" value. 1.00 is a perfect correlation, and 0.00 is no correlation whatever. The r value for week-to-week TSH levels was a mere 0.17—just a teensy bit (17%) above no correlation at all. The r value was not statistically significant. This means that the very weak positive correlation week-to-week could have been due merely to chance similarities in the TSH levels, and there may actually have been no correlation at all.[38] Another way of looking at this is that patients' TSH levels significantly differed week-to-week.

A Japanese researcher studied variations in TSH levels in normal and depressed men and women. He reported, "A large intra-individual variation [variations in the same person] of serum TSH levels determined on different days was found equally in both men and women." He also reported, "The present study demonstrated a large variation of TSH levels in various conditions, even in the same individuals . . . ."[42]

Still other researchers, Weete and colleagues, reported significant variations in the levels of the free T4 and TSH in normal men—levels Dr. Guttler assumes to be impeccably consistent. Variations in the levels of the hormones, however, are of great enough magnitude to lead to misdiagnoses of patients' thyroid status. The researchers reported that from day to night, men's TSH levels increased an average of 140%. Their free T4 levels increased by 7%. The researchers also took blood samples every five minutes in a six-to-seven hour period starting between 7 pm and 10 pm. On average, the free T4 level varied by 11%, the free T3 by 15%, and the TSH by 13%. The researchers reported that "a significant regular variation" in the levels of the hormones occurred every 30 minutes.[39]

Aside from natural variations in TSH levels, the levels may vary according to other factors, such as lost sleep or absorption of thyroid hormone into the blood. When normal women were partially deprived of sleep, their TSH concentrations increased significantly. The levels remained high through the following day.[40] Sleep deprivation is so common nowadays that it's likely that many patients' TSH levels are tested the day following a night of insufficient sleep. This study suggests that their TSH levels may be higher than they would be following a night of enough sleep. This variation in TSH levels could easily lead doctors to misdiagnoses[25] if they aren't cognizant of the effect of too little sleep and inquire about it when they test a patient's TSH level.

After a patient takes a dose of T4, her free T4 level remains elevated for some 9 hours. In patients taking T4-replacement, the T4 level was increased an average of 13%. The TSH level in these patients was decreased by 19%.[41] Obviously, if a patient's blood is drawn during this 9-hour time, the decision her doctor makes about a dosage adjustment may be quite different from the one he would make if her blood is drawn after the 9-hour period.

Based on this finding, the following scenario is highly likely to occur in the clinic of an endocrinologist. Like a quasi-accountant, this endocrinologist bases his decisions *strictly* by the numbers—by the patient's lab test levels.[25]

A man who works out five days a week at a gym comes to the endocrinologist's clinic complaining of depression, fatigue, and weight gain. The doctor measures the man's TSH and free T4 levels. His TSH level is 3.05—a hair above the new upper limit according to the American Association of Clinical Endocrinologists. His free T4 is 59.0, which is the lower limit. Based on these levels, the technocratic doctor gives the man a diagnosis of hypothyroidism and attributes his symptoms to a thyroid hormone deficiency. The doctor prescribes a small amount of T4—just enough to lower the man's TSH level below 3.03 and raise his free T4 slightly.

Contrast the above outcome with the following likely result had the man come in thirty minutes later. The endocrinologist measures the man's TSH and free T4 levels. As the Weete study found,[39] the TSH may vary 13% every half-hour. In line with this, thirty minutes later the man's TSH level is 13% less than in the first scenario; it is down from 3.05 to 2.65.

The endocrinologist also measures the man's free T4 level. Recall that Weete found that men's free T4 levels varied 11% in thirty-minutes.[39] The man's level now—thirty minutes later than in the first scenario—is up by 11%; it's no longer 59.0, but 64.9. Based on these TSH and free T4 levels, the technocratic doctor tells the man that he's *definitely not* hypothyroid and that his symptoms must be caused by some other disorder. For the man's depression, the endocrinologist recommends a psychiatrist; for his fatigue, more sleep; and for his weight gain, more exercise.

The studies I've cited in this section should make my point clear: Dr. Guttler's trust in the perfect consistency of free T4 and TSH levels is misplaced. Over the years, I've talked with scores of doctors whom Dr. Guttler would consider "real thyroid doctors." I've done so with a keen interest in their approach to diagnosis and treatment of hypothyroid patients. From those conversations, I've come to believe that in their clinical decisions, most of these doctors do *not* allow for factors such as short-time variations in hormone blood levels, too little sleep, or ingestion of thyroid hormone. Because their clinical decisions depend *solely* on the levels of the two hormones without consideration of other factors, I've never trusted their clinical decisions. Nor, for the same reason, could I trust Dr. Guttler's.

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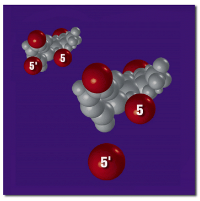

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Debate

Pregnant Women and Their Newborns: Among the Victims of T4 Replacement

Dr. John C. Lowe

Director of Research: Fibromyalgia Research Foundation

Correspondence: Dr. John C. Lowe
drlowe@FibromyalgiaResearch.org, drlowe@drlowe.com, 603-391-6061

Introduction

A gynecologist recently contacted me out of concern for his pregnant wife and their gestating baby. His wife is hypothyroid and her endocrinologist is adamant that she should not use any approach to thyroid hormone therapy other than T_4 replacement. The gynecologist said that his wife's fatigue has improved with the treatment, but she's still mildly fatigued. And like many other patients on T_4 replacement, she has had no improvement whatever in other symptoms that she developed for the first time soon after she underwent a thyroidectomy.

The wife's persisting symptoms include dry skin, cold hands and feet, and depression. She also cannot lose an extra 15 lbs (6.8 kgs) she gained within six months after starting T_4 replacement. The gynecologist gave the endocrinologist a copy of an article I wrote for *Thyroid Science*[1] in which I cited studies that show that patients on T_4 replacement gain weight they cannot lose. Of course, this attempt to educate the endocrinologist was to no avail. Still, he was adamant that the wife use no approach to thyroid hormone therapy other than T_4 replacement. The gynecologist and his wife sat and listened to the famous refrain of endocrinologists: "You just need to diet and exercise." And they witnessed his mind close tightly, like a pupil exposed to light, when they informed him that she doesn't over eat and she works out at a gym six-days each week.

Fortunately, the gynecologist saw that the endocrinologist is a fanatical devotee not of his wife's welfare but of T_4 replacement. He phoned me after making an appointment for his wife with a local natural medicine doctor who is well known for treating patients with natural desiccated thyroid.

The reason the gynecologist contacted me is that he was bothered about a report he had read. The report was published in a Scandinavian medical journal on obstetrics and gynecology, one of the journals he reads to keep up on research in his specialty.[5] His impression was that the study, conducted in Sweden, showed that hypothyroid women and their newborns were likely to have health problems as a result of the mother's hypothyroidism—*despite* her undergoing thyroid hormone therapy. He feared that even if his wife begins using desiccated thyroid, she and their developing baby are at risk of harm.

After reading the report, I phoned him back. I asked him to carefully consider what the study actually showed. The women in the study and their newborns did not develop health problems *despite* thyroid hormone therapy; they did so *because of* the type of thyroid hormone therapy they used. That therapy was T_4 replacement.

The study didn't involve approaches to thyroid hormone therapy other than T_4 replacement. But based on many years of clinical experience with pregnant hypothyroid women, I believe the gynecologist will have saved his wife and their baby from potential harm by switching from the endocrinologist's treatment to that of the natural medicine doctor.

Swedish Study of Women Who Used Thyroxine

The Swedish study included pregnant women on thyroid hormone therapy and their newborns. Some of the women reported using thyroid hormone early in their pregnancies and others received prescriptions for thyroid hormone late in their pregnancies. The total number of these women was 9,866. Their infants totaled 10,055. The women who used thyroid hormone therapy during their pregnancies were compared to all women in the Swedish population who gave birth during the same time span (July 1, 1995 to December 31,

2004) and their newborns.

It's important to note that the women in the study used "thyroxine," which is also called "T_4." And with a high degree of probability, the women were restricted to replacement doses of T_4, that is, doses that kept their TSH levels within the current reference range in Sweden.

The purpose of the study was to learn whether women who took thyroid hormone during their pregnancies and their newborns faired better or worse than women who didn't take thyroid hormone and their newborns. The researchers looked for any adverse effects, such as congenital malformations among the newborns and pregnancy complications among the mothers.

Compared to women who didn't use T_4 during their pregnancies, the women who did had a higher rate of preeclampsia. They also had more preexisting and gestational diabetes, cesarean sections, and they required more inductions of labor. And preterm birth was "marginally increased" among the women who used T_4.

Eight of the women's infants had neonatal thyroid disease. Seven had "thyreotoxicosis," but a description of the other infant's disease wasn't available. *A statistically significant number of the infants had congenital malformations*.

The researchers' conclusion was, "Women on thyroid substitution during pregnancy had an increased risk for some pregnancy complications, but their infants were only slightly affected."[5] A more accurate conclusion is this: Both women restricted to T_4 replacement and their newborns had a statistically significant higher incidence of abnormalities.

The researchers, of course, didn't take their results as an indication that T_4 replacement didn't protect the health and well-being of the pregnant hypothyroid women and the newborns. But that's truly what the results mean, for if T_4 replacement were an effective substitute for the women's own internally-produced thyroid hormone, they and their newborns would have had no more abnormalities than the other women who didn't use thyroid hormone. The culprit in this unfortunate case is the T_4 replacement the Swedish women were restricted to; *T_4 replacement is simply inadequate for and thus harmful to a significant percentage of newborns and their mothers during their pregnancies.*

Harm from Inadequate Thyroid Hormone Treatment During Pregnancy

It is clear that if a pregnant women isn't treated at all for hypothyroidism, her newborn is likely to be harmed. The most commonly cited adverse effects in newborns are brain abnormalities and resulting psychological symptoms. Also, when the mother is hypothyroid during pregnancy, the *severity* of her thyroid hormone deficiency is likely to be proportional to the harm done to her newborn.[3][4]

That the severity of the mother's hypothyroidism is related to the degree of harm to her newborn means this: The newborn is likely to suffer adverse effects not only if the mother does not use thyroid hormone at all during the pregnancy, but also if her therapy is inadequate. It's a matter of degrees.

In a pediatric study in Italy, newborns with congenital hypothyroidism had impaired psychological function, despite them being treated with T_4 replacement. When their doctors treated them with T_4/T_3 replacement, the infants' psychological impairment did not improve.[2] *Obviously, "replacement" doses—that is, doses that kept the infants' TSH levels within the current reference range in the region of Italy where the study was done—were inadequate for relieving impaired psychological functioning that resulted from their congenital hypothyroidism.*

My question is, If these infants had been treated with higher dosages, would these dosages have relieved their impaired psychological function? The pediatricians who conducted the study noted that the two replacement therapies [T_4 and T_4/T_3 replacement] were inadequate to ensure normal brain development in the infants: ". . . in our experience, the 2 types of treatment, at least at the doses we used, show the same efficacy but are not optimal in an early normalization of the neuropsychological performances of CH [congenitally hypothyroid] infants."[4,p.1059]

Yet the pediatricians expressed apprehension of using higher dosages. They wrote, for example, ". . . the fear of provoking undesired side effects and the lack of any reference data in the literature for infants in the first months of life prompted us to use doses of T_3 that may have been insufficient and a T_4:T_3 ratio that was not perhaps optimal."[4,p.1059]

These pediatricians' reasons for not using higher doses of T_3 seem reasonable. But to me, the reasons appear to be face saving. The reason I say this is that the policy that dominates other conventional medical specialities also dominates in pediatric care. That policy is "nothing risked, nothing gained," so assertively treat patients with drugs even when there is substantial evidence that they may harm them patients.

This policy, if applied to thyroid hormone therapy—which unlike most pharmaceutical therapies is harmless even when most patients' TSH levels are suppressed[6]—might have salvaged the infants' psychological functioning. But another factor the pediatricians didn't mention almost certainly caused them to use only the replacement approach—*despite them reporting that the infants remained psychologically impaired!*

That factor is the risk of brutal consequences for using a thyroid hormone therapy other than replacement. For clinicians in most parts of the world today to use doses of thyroid hormone higher than replacement doses risks punitive results that enforcer endocrinologists ensure medical regulatory boards will doll out to the clinicians. The risk of those dreaded consequences intimidates most clinicians into using only replacement doses. And the clinicians' compliance ensures that vast rivers of revenue continue to flow to Big Pharma from the sale of scores of millions of TSH assays.

Conclusion

A statistically significant percentage of the mothers and their newborns in the Swedish study suffered harm because T_4 replacement was ineffective for them. The harm to them may have been worse had the mothers had no thyroid hormone therapy at all. Then again, for some patients, T_4 replacement is little better than no treatment at all. For many others, it's helpful but far from fully effective, and therefore harmful.[6]

It's possible, then, that effective thyroid hormone therapy would have protected the Swedish mothers and infants from the harm they suffered from T_4 replacement. Of course, as I said, the pediatricians didn't test any alternate thyroid hormone therapy in the study. What is important is that the study showed that T_4 replacement harmed many mothers and their newborns. This proof of harm from T_4 replacement would compel me to ask my hypothyroid wife, were she pregnant, to gamble on another approach to thyroid hormone therapy. The gynecologist feels the same way, and his wife will soon see the local natural medicine doctor.

It's often hard for me to bear that adults are commonly harmed by the ineffectiveness of T_4 replacement. *But newborns, too?* In my firm opinion, subjecting newborns to harm by restricting their hypothyroid mothers to T_4 replacement isn't just a scientific and humanitarian issue; to me, it's also a moral one.

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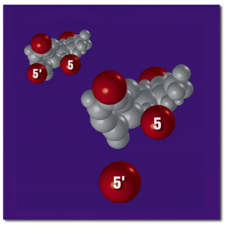
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The Linguistic Etiologies of Thyroxine-Resistant Hypothyroidism

Eric K. Pritchard

(Full Text Free in pdf format)

Contact: Eric Pritchard, ekpritch@earthlink.net

ABSTRACT. The thyroxine resistant victims of hypothyroidism are not suffering because there is no treatment available—the Food and Drug Administration approved and indicated them long ago. These victims are suffering because the proper treatments are not considered—linguistic etiologies keep the science of "exo-endocrine" (outside of the endocrine system) hypothyroidism beyond the reach of the practicing physician with the confusion of "overinclusion" (identical treatment of two classes that burdens one excessively). This confusion begins with two definitions for "hypothyroidism," thyroid-centric" and "symptom-oriented," which are related to thyroxine (T4) and triiodothyronine (T3), respectively. Although the hypothyroidism paradigm concentrates upon the thyroid and thyroxine, the active hormone in the tissue cells is triiodothyronine. The claimed intimate relationship between inadequate thyroid secretion and the symptoms of hypothyroidism has been distanced by scientific discoveries of exo-endocrine hormone operations. Symptoms do not imply endo-endocrine (within the endocrine system) etiologies *only* anymore.

The confusion of overinclusion hides the exo-endocrine hormone operations, their potential for failure, and their importance. Different hormones and etiologies demand different diagnostics and hormone supplements.

The confusion of overinclusion continues in the coverup for thyroxine-resistant treatment failures. Counter intuitively and contrary to research, laboratory assays and the exo-endocrine hormone operations are declared infallible. Fallacious logic reassigns continuing symptoms to "normal" somatic etiologies. Definition confusion allows endo-endocrine test results to be erroneously applied to exo-endocrine etiologies.

Baisier, et al., published an empirical study of thyroxine resistant patients and found success in using an indicated, FDA approved, and available therapy. These sufferers need the resolution of this confusion so they can regain their lives. The linguistic etiologies must be eliminated so that people needing different treatments are treated differently and properly.

KEY WORDS. hypothyroidism, exo-endocrine, thyroxine-resistant, Baisier, continuing symptoms, basal temperature, nonspecific symptoms, combination therapy, guideline, overinclusion.

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INTRODUCTION

The victims of hypothyroidism who are thyroxine resistant are not suffering because there is no treatment available—the Food and Drug Administration approved and indicated them long ago. These victims are suffering because the proper treatments are proscribed by the endocrine establishment, its paradigm, and its treatment guideline. Consequently, they are rarely considered. The proper treatments are not considered because linguistic etiologies keep the "medical science" of exo-endocrine hypothyroidism (hypothyroidism caused by etiologies outside of the endocrine system) beyond the rationale of the practicing physician by improperly (over) including them with endo-endocrine hypothyroidism (hypothyroidism caused by etiologies within the endocrine system). The first etiology is in the title: "Thyroxine-Resistant Hypothyroidism." The second is in the description: "exo-endocrine hypothyroidism."

The endocrine establishment would claim that both are oxymorons. But are they? That depends upon the definition of "hypothyroidism." Is it thyroid-centric or symptom-oriented? This essay explores the consequences of these choices in the light of the physiology to show that the thyroid-centric is only applicable to the recognized class of endo-endocrine hypothyroidism, while the symptom-oriented definition is applicable to both endo-endocrine hypothyroidism and the unrecognized class of exo-endocrine hypothyroidism.

Patient suffering should be sufficient to demand the linguistic treatment of these etiologies. But it has not. Many respondents to a minuscule outreach effort[32] have been suffering for decades. However, since medical guidelines are used by state boards of medicine to regulate, discipline, and prosecute physicians, the notion of Overinclusion, a derivative of the Equal Protection Clause of the Fourteenth Amendment and the antithesis of Due Process, appears to be applicable and compelling. [see the definitions below]

The physiology of hypothyroidism begins within the endocrine system (the hypothalamus, the pituitary, and the thyroid) continues through the exo-endocrine peripheral metabolism sites in various organs (predominately, the liver) to the hormone receptors of the peripheral cells, where the hormones are used and the symptoms begin to be sensed. Certainly, symptoms are not produced directly by any hormone when in the serum. Since the assays are serum based, they are indirect measurements. The subsequent conclusions, then, depend upon inferences and correlations.

The history of hypothyroidism begins after the discovery of hyperthyroidism with the discovery of thyroid extract in 1891, the realization that the thyroid controlled the metabolic rate in 1895, and Hashimoto's disease in 1912. The structure of thyroxine (T_4) was discovered in 1926 and triiodothyronine (T_3) was identified in 1952. By the time that the exo-endocrine peripheral conversion of T_4 to T_3 was discovered in 1970, sufficient time had passed for the hypothyroidism paradigm to form and solidify. This paradigm includes the rigid belief that there was an intimate connection between the thyroid secretion and symptoms. Thus, all hypothyroidism etiologies were believed to belong to the same class. However, the thyroid and symptoms were separated by the discoveries, in 1967 and 1970, of two intervening hormone operations, the exo-endocrine peripheral conversion of T_4 to T_3 and the identification of T_3-binding receptors in tissue. Then in 1989 and 1990, mutations in the thyroid-hormone receptor accounted for increasing hormone reception resistance.[1] Thus, there are exo-endocrine etiologies for the symptoms of hypothyroidism. Unfortunately, they are substantially ignored and hypothyroidism remained singularly classed in spite of significantly different etiologies, different diagnostics, and different hormone supplements.

MULTIPLE, UNDECLARED DEFINITIONS OF HYPOTHYROIDISM

The inevitable tension created by the peripheral conversion and subsequent exo-endocrine discoveries are reflected in the once believed similar, but now distinct definitions for "hypothyroidism." The thyroid-centric definition is quite similar to the definition of "hypothyroid": "The clinical consequences of inadequate secretion of hormones by the thyroid." The symptom-oriented definition removes the intimate connection between the thyroid gland and symptoms: "The clinical consequences of inadequate levels of thyroid hormones in the body." (Taber's Cyclopaedia Medical Dictionary) And that definition may be reasonably and should be extended to "The clinical consequences of inadequate *usage* of thyroid hormones by the body"—particularly in light of the finding of Baisier, et al. that a 24-hour urine diagnostic correlates best[2] or Brady's preference for the rT_3 test.[3]

A fallacious attempt was made to mitigate this tension by contextually assuming the infallibility of exo-endocrine hormone operations.[4] However, not only is this somatic infallibility quite counter intuitive, but predating research[5][6] disputes this contextually alleged perfection. The tension is valid since the definitions have different associations. The thyroid-centric definition, being similar to "hypothyroid," is more related to the secretion of thyroxine (T_4). On the other hand, the symptom-oriented definition is more related to the availability or usage of triiodothyronine (T_3) as suggested by the following quotation:[7]

> *"T_4 . . . is not the active ingredient. T_3 is the active ingredient, and it's the thing that accounts for the thyroid hormone action. As I've been reminded many times, there are no intracellular events that we know that can be described by T_4 at the level of the nucleus. Only T_3. T_4 is not the active compound. Likewise, the site of action is in the nucleus. The site of action is not T_4 in the plasma."* –-Dr. E. Chester Ridgway

As a consequence of no intracellular events being directly related to thyroxine, the implications of the apparently similar definitions are significant. The thyroid-centric definition ignores the potential of exo-endocrine etiologies while the symptom-oriented definition is inclusive of both endo- and exo-endocrine etiologies. Thus, the following lament by Anthony Taft and Geoffrey Beckett[8] is, then, quite understandable:

> *"It is extraordinary that more than 100 years since the first description of the treatment of hypothyroidism and the current availability of refined diagnostic tests, debate is continuing about its diagnosis and management."*

This lament is even more understandable by the author's research of dictionary definitions of "hypothyroidism." There were 29 citations for the thyroid-centric version and 22 citations of the symptom-oriented. However, to seemingly sustain the confusion, 11 of each were cited simultaneously. Confusion reigns.

Overinclusion reigns. Since the dominate endo-endocrine hormone is thyroxine (T_4) and the dominate exo-endocrine hormone is triiodothyronine (T_3) and since their etiologies are different, the treatment of these etiologies are different, these forms of hypothyroidism should be divided into two classes: endo-endocrine and exo-endocrine hypothyroidism. There is precedent for this concept, type 1 diabetes which suffers from the lack of insulin and type 2 which suffers from the inability to use it. This is quite similar to endo-endocrine hypothyroidism not producing sufficient thyroxine and exo-endocrine hypothyroidism not being able to use it by deficient peripheral metabolism or deficient hormone reception.

Then, this dense fog of overinclusion confusion is maintained. Inspect the only closest applicable guideline.[9] The choice of definitions for "hypothyroidism" is not indicated (or stipulated, see definitions), but the text implies both. The guideline description of symptoms implies the broad, symptom-oriented definition. But, the limited diagnostics and treatments in the guideline imply the narrow thyroid-centric definition. If the practicing physician has a thyroxine-resistant patient with persistent symptoms of hypothyroidism in spite of thyroxine treatment and euthyroid-indicating serum levels, the physician is left in a quandary. There is no other recommended treatment. This leaves the physician with two choices:

(1) Adapt the standard practice excuses provided by the admonition against any treatment containing T_3,[4][9] deny the existence of continuing hypothyroidism, and deny the potential existence of a second class of hypothyroidism—exo-endocrine hypothyroidism. In this way, the physician avoids the potential wrath of a board of medicine inquiry. The physician wins, but the suffering patient loses.

(2) Recognize that the excuses for thyroxine-only treatment failures are fallacious, exercise the treatment disclaimer ("In general . . . ", page 6, left-hand column of[9]) and the completeness disclaimer at the end of the guideline (page 9 of [9]), and successfully treat the patient with a hormone replacement that is specifically discouraged and proscribed, but is applicable to a second class of hypothyroidism—exo-endocrine hypothyroidism. While the patient wins, the physician loses to the liability of the draconian wrath of a board of medicine for unnecessarily exceeding the recommended treatment (as measured by inconclusive diagnostics, see below) and endangering the patient since they believe that there is only one class of hypothyroidism victims.

Linguistic etiologies create this quite unprofessional win-lose situation. First, the guideline[9] does not specify or stipulate which definition is operative. If the definition were specified, as required by protocol,[27] the patient-physician relationship would become win-win for either of the following two reasons:

(1) If the thyroid-centric endo-endocrine-only definition were specified in the guideline,[9] then the physician and the board of medicine would realize that the guideline did not apply to the thyroxine resistant, exo-endocrine patients. The physician could then treat the patient properly without fear of fallacious hypothyroidism guideline action by a board of medicine.

(2) If the symptom-oriented definition were specified in the guideline[9] and the guideline maintained logical consistency, then the physician would be appropriately guided by an expanded and revised guideline that addressed both classes of hypothyroidism. The patient would be treated properly without fear of fallacious action by a board of medicine.

LOGICAL FAUX PAS

The lack of definition for hypothyroidism and the lack of recognition of a second class of hypothyroidism are hardly the last linguistic faux pas in this realm. For example, the guideline (the lower, right-hand column of page 6 of [9]) refers to a dispute between studies of combinations of thyroid hormones. Some studies[10][11][12][13] take advantage of the lack of definition of "hypothyroidism," to form the studies and then to make overly broad conclusions or inspire overly broad interpretations. Using subjects with primary hypothyroidism is not representative of subjects with deficient peripheral metabolisms or increased peripheral hormone receptor resistance because they are physiologically different. Concluding that a T_3-containing treatment is of no use is not proper when only most showed no improvement. The difference between "all" and "most" is "rare" or "few," precisely the occurrence rate of thyroxine-resistant, exo-endocrine hypothyroidism, the other class of hypothyroidism victims. Thus, in either case, professionalism and patients are not served properly.

If the definitions were known, then those studies could be properly categorized according to the classes of hypothyroidism. The detractions to combination hormone treatments are formulated under a narrow definition of hypothyroidism, endo-endocrine hypothyroidism, and their conclusions must be so treated and limited. The proponents of combination hormone treatments[14][15][16][17][18] are formulated under a broad definition of hypothyroidism and their conclusions must be examined in a different, inclusive light.

For example, "Thyroid Insufficiency? Is Thyroxine the Only Valuable Drug?"[2] primarily deals with the thyroxine-resistant patient, i.e., those that fall within the broad, symptom-oriented definition of hypothyroidism but that fall outside of the narrow, thyroid-centric definition, i.e., exo-endocrine hypothyroidism. As a consequence, the conclusion of successful treatment for the thyroxine-resistant patients should only apply to the thyroxine-resistant, although this particular study also treated undelineated patients in the same way with success. Baisier, et al., had success with both classes of hypothyroidism because they used natural desiccated thyroid, which does address both classes of hypothyroidism.

In spite of the success by Baisier, et al.[2] in diagnosing and treating thyroxine-resistant patients, the expression of the paradigm,[4] made the errant assumption that no one could be thyroxine resistant because the peripheral metabolism was "regulated" and contextually infallible. Although this "regulation" was refuted by counter examples in the literature[2][5][6] ([2] by inference), these counter examples are simply ignored. They are ignored because it is human nature to preserve paradigms.[19] People want the consistency of prior decisions, i.e., *starie decisis*.

The expression of the hypothyroidism paradigm[4] also takes advantage of other logical faux pas to cover up or explain away the failures of thyroxine (T_4) only therapies. The first cover up discredited the basal temperature diagnostic found by Barnes[14] and used by many others. However, this was falsely discredited by citing a study by Mackowiak.[20] Mackowiak had not excluded subjects with hypothyroidism. Thus, the lower basal temperature diagnostic was attempted to be dissociated from hypothyroidism with a conclusion influenced by hypothyroidism. This logical faux pas is a form of a circular argument and consequently proves nothing.

Similarly, the paradigm expression[4] attempts to reassign somatic symptoms when the thyroxine treatment for hypothyroidism fails by describing them as "nonspecific." This attempt cited Barsky[21] who also did not exclude subjects with hypothyroidism and consequently used a conclusion influenced by hypothyroidism to dissociate a connection with hypothyroidism. Additionally, Baisier, et al.,[2] presents a counterexample in the form of an accurate somatic diagnostic technique based upon a combination of coarse evaluations of each of eight somatic symptoms. First, this clinical evaluation values each of the eight symptoms with 0, 1, or 2 for none, some, and substantial presence. Second, these valuations are summed for an overall value between 0 and 16 inclusive. Finally, the sum of these eight clinical evaluations is compared to limits. The ranges of values for euthroid subjects and those with hypothyroidism are substantially separated. Therefore, symptoms, although in combination, can successfully diagnose hypothyroidism—a substantial counter-example to the hypothyroidism paradigm.

Thus, the establishment deflection of blame for the failures of the single-class, thyroxine-only prescription[9] is both illogical and disproved.

Further, neither the guideline[9] nor the paradigm expression[4] acknowledges the existence of any syndrome of the resistance to thyroid hormones[22][23] or its potential for treatment.[24] There are hormone receptors everywhere. Any abnormality in the reception at the glands or organs is indistinguishable from immediately subsequent hormonal operation abnormalities. However, in the peripheral cells, the abnormality is the basic operation of the cell and the creation of symptoms.

MEDICAL FAILURES HIDDEN BY THE CORRUPTION OF EVIDENCE-BASED MEDICINE

The failure of the thyroxine-only treatment prescription is made more confusing by enshrining its short comings in the gold standard of a laboratory assay protocol. This corrupts the vaunted Evidence-Based Medicine protocol.[25] Such a corruption is promoted by the now-discredited, mind-distrusting Behaviorist philosophy[26,p.19] and ignores the "checks and balances" counsel of governance of the great James Madison:

> "*That if all men were angels, no government would be necessary. If angels were to govern men, neither external nor internal controls on government would be necessary. In framing a government which is to be administered by men over men, the great difficulty lies in this: you must first enable the government to control the governed and, in the next place, oblige the government to control itself.*" —*The Federalist Papers*

This corruption of Evidence-Based Medicine defies the non-angelic fallibility of mankind as it assumes that every element of the test from its creation and the establishment of normality to the delivery of test data is always perfect. The excessive faith in this illogical corruption is a substantial component in the systemic maltreatment of the victims of thyroxine-resistant, exo-endocrine hypothyroidism. It improperly keeps physicians from listening to their patients and considering the validity of their symptoms. It improperly claims people do not have "thyroid" hormone issues when it does not measure the results of where the action is:[7] in the *intracellular* spaces or any result or indication thereof.

Counter Examples

The author knows of two people presenting counter-examples to the thyroid-stimulating hormone concepts: (1) A subject with an extreme hyperthyroidism indicating TSH level of 0.002 exhibits clinical hypothyroidism; (2) A subject with a substantial hypothyroidism indicating TSH level of 60 exhibits clinical hyperthyroidism.

The thyroid paradigm cannot explain these characteristics, however, deficiencies and excesses in the exo-endocrine behaviors can. The failure of the thyroid-stimulating hormone paradigm to explain these counterexamples demands consideration of a second class of "thyroid" etiologies—exo-endocrine etiologies.

THE ETIOLOGIES OF LINGUISTIC ETIOLOGIES: NON-COMPLIANT GUIDELINES

The etiologies of linguistic imprecision stem from the apparent assumption that the problem does not exist. The immediate guide to medical authors, *The Manual of Style*, produced by the American Medical Association, does not mention the concept beyond a single sentence admonition for clarity. It spends scores of pages upon abbreviations and statistics but only one sentence for clarity. Unfortunately, *The Manual of Style* is not alone. Other such manuals are also quite lacking in lessons of clarity. More unfortunately, the etiologies of vagueness are generally not explored in the classroom. Somehow, clarity is supposed to arise in the mind like wild flowers in the spring—naturally.

The protocols for the authorship of the guidelines have been written, even by the authoring organization of the hypothyroidism guideline[27][9] but were ignored. The most important admonition to this case that is in the protocol[27] but is not written into the guideline:[9] the stipulation of definitions of critical and readily misunderstood words and terms [see the definitions].

Studies of the authorship of medical guidelines have shown them to be substantially lacking. Dr. Shaneyfelt, et al., gave an average grade of 43% to 279 medical guidelines.[28] Dr. Grilli, et al., found that only 5% of 431 guidelines met all three criteria of their grading system and that most were unsatisfactory.[29] Dr. Burgers, et al., graded 100 guidelines and found that oncology guidelines were better (42.2%) than other guidelines (29.4%).[30]

Additionally, a study[31] estimates that 4% of all hospital patients will suffer from an "adverse" event that produces an estimated 200,000 deaths annually. Since half were preventable and a fourth are negligent, then the remaining causes are either beyond medical science or merely beyond practice guidelines, or in the confusion within practice guidelines.

Since it appears that human suffering is an inadequate motivation to transform vagueness to clarity, perhaps the civil rights guaranteed by the Constitution of the United States will. When medical missives meet the law at the governments' boards of medicine, the concept of "Overinclusion," a derivative of the Equal Protection Clause of the Fourteenth Amendment, becomes applicable. (See the definitions, below.) Overinclusion occurs when two distinct classes, of different etiologies that require different treatments, are included in the same class and the treatment for one of these classes is improper and consequently places undue and excessive burden upon the members of that class.

Certainly, the inconsistent implications of the two implied definitions of "hypothyroidism" in the guideline[9] and the expression of the paradigm[4] creates two classes, those people included in the narrow definition and those included in the broad definition but not included in the narrow definition. There is an endocrine precedent: While excessive urination is a general symptom of diabetes, its somatic nature separates the various distinct subclasses. The major subclasses, type 1 and type 2, are similar to the classes of hypothyroidism: the inability to produce and the inability to use respectively.

CONCLUSIONS AND FINAL IMPLICATIONS

Baisier, et al.[2] have empirically shown that thyroxine-resistant patients exist, can be treated properly, and regain their former selves with natural desiccated thyroid. This original treatment for hypothyroidism[1]has served many quite well[14][18] in the past and presently. Other forms of combination therapies have been used successfully as well.[16][17] The Baisier, et al., empirical results are not flukes. Physiological theory agrees. The exo-endocrine hormone operations, peripheral metabolism and peripheral hormone receptors, exist and are fallible. [5][6][22][23][24]

Accepting the fallibility of exo-endocrine operations upon the thyroid hormones, which common sense and science demands, also demands acceptance of the treatment with the active exo-endocrine hormone, triiodothyronine (T_3), simply because that is the hormone that requires replacing in case of such failings. Unfortunately, the oligarchical powers bestowed on the medical associations via the state boards of medicine have far greater influence over physicians than truth and reality. Of the 120 plus thyroxine-resistant sufferers found by our minuscule outreach effort—letters to the editors of West Virginia newspapers,[32] only six have been able to use our research to persuade their physician to prescribe any physiologically necessary T_3-containing therapy.

Hopefully, the Equal Protection of the citizens of the United States, guaranteed by the Fourteenth Amendment to the Constitution and Due Process, will, as it should, prevail. Hopefully, the existing Overinclusion of all hypothyroidism victims into a single class will demand an end to the linguistic etiologies that imprecisely treat all types of victims in the same way. Hopefully, the seemingly endless suffering by thyroxine resistant patients will end with their return to energetic lives by the proper treatment of exo-endocrine hypothyroidism.

Hopefully too, the linguistic methodology shown herein will spread throughout medicine to improve guidelines and medical care.

Albert Einstein recommends that problems be simplified to clarify them. However, they cannot be overly simplified, since that creates a different type of confusion. The early lack of knowledge plus the use of universally applicable natural desiccated thyroid gave single-class hypothyroidism credence. This over simplification became evident with the advent and use of levothyroxine sodium. Levothyroxine sodium left some hypothyroidism (broad, symptom-oriented definition) victims untreated, thereby demonstrating the confusion of over-simplification and overinclusion. Thus, the use of levothyroxine sodium exposed the existence of a second class of hypothyroidism victims—those with exo-endocrine hypothyroidism, who have different physiological etiologies that physiologically, rightfully, and lawfully demand different treatments.

DEFINITIONS

due process The conduct of legal proceedings according to established rules and principles for the protection and enforcement of private rights, including notice and the right to a fair hearing before a tribunal with the power to hear the case.

endo- A prefix meaning within or inside of.

exo- [Gr. exo, outside] Combining form meaning without or outside of.

equal protection The constitutional guarantee under the 14th Amendment that the government must treat a person or class of persons the same as it treats other persons or classes in like circumstances.

hypothyroidism Thyroid-centric meaning: the clinical consequences of inadequate secretion by the thyroid. Symptom-oriented meaning: the clinical consequences of inadequate levels or usage of thyroid hormones. Potential future meaning: The clinical consequences of inadequate usage of thyroid hormones. [This definition encompasses all etiologies of hypothyroidism.]

overinclusion Extention beyond the class of persons intended to be protected or regulated; burdening more persons than necessary to cure the problem. [Legally this concept requires judgement based upon the percentage of persons overincluded, the extent of their burden, and the potential for removing the burden.]

proscribe Outlaw or prohibit; to forbid

starie decisis [Latin for "to stand by things decided"] The doctrine of precedent, under which it is necessary for a court to follow earlier judicial decisions when the same points arise again in litigation.

stipulative definition A definition that, for the purposes of the document in which it appears, arbitrarily clarifies a term with uncertain boundaries or that includes or excludes specified items from the ambit of the term.

vagueness Uncertain depth of meaning. Vagueness raises due-process concerns if legislation does not provide fair notice of what is required or prohibited, so that enforcement may well become arbitrary. [However, amazingly, vagueness can be eliminated if there is a consensus in the community of the meaning.]

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ABOUT THE AUTHOR

Eric K. Pritchard has degrees in mathematics and electrical engineering and more than forty years of experience in these fields. He has thirty-nine U.S. Patents in seven disciplines, some of which also have foreign counterparts. After researching and designing circuits to operate through a strategic nuclear threat, he began researching and designing solutions for specialized production problems. The "impossible" task of translating the artistry of vacuum tube amplifiers to solid state, a task that many had tried and all failed, intrigued him and ultimately demanded a reinspection of engineering theory.

According to Pritchard, "Like medicine, engineering predominately fails to maintain a tightly logical connection with firm knowledge. Unlike mathematics, both make sweeping assumptions and approximations, use imprecise arguments, and readily excuse failures. Although failures in engineering usually only cost money, failures in medicine cause or extend pain and suffering and can cause or hasten death."

Mr. Pritchard began studying the etiologies of and treatments for hypothyroidism after his wife recounted to him visits with physicians that suggested "an errant philosophical structure in the diagnosis and treatment of hypothyroidism." He writes, "This suggestion was made by the excessive dependence upon the 'objective' laboratory assay and the total depreciation of the 'subjective' clinical presentation. The laboratory assay claimed euthroidism while the clinical presentation disagreed completely. From earlier research in audio, where the objective and subjective clash also and where the 'objective' is overly glorified and the "subjective" is under appreciated, the existence of an errant technical assumption was probably being hidden by the excessive valuation of 'objective' testing. Just as the audio paradigm assumes that the human hearing process does not produce harmonics of audible tones, the endocrine paradigm assumes that all somatic operations on 'thyroid' hormones outside of the endocrine system are infallible. Just as the audio paradigm made the Total Harmonic Distortion test and the Intermodulation test the gold standard of objectivity, the endocrine paradigm made the thyroid-stimulating hormone (TSH) test its gold standard." Pritchard poignantly concludes: "The difference between these situations is substantial. The audio debate does not adversely affect health."

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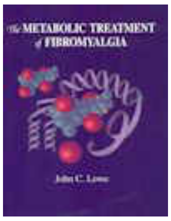

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Latest Updates to drlowe.com

B Complex Vitamins Synergists in the cellular actions of thyroid hormone.	Taking thyroid hormone increases the amounts of some B vitamins that cells use.	Everyone taking thyroid hormone should take a B complex vitamin supplement.
#6 Super B	Take with food	One tablet two times each day.
• B-1 (Thiamine mononitrate) (50mg)	• B-6 (pyridoxine hydrochloride) (50mg)	• Biotin (400mcg)
• B-2 (Riboflavin) (50mg)	• B-12 (cyanocobalamin) (100mcg)	• Folic Acid (400mcg)
• Niacinamide (300mg)	• Pantothenic acid (Calcium D-pantothenate) (100mg)	
Carotenoids	Antioxidant nutrients.	Occur naturally in plant foods.
#351 Carotenoid Complex • A mixture of carotenes as they occur in nature. They provide a variety of antioxidant protective nutrients for various parts of the body. (See alternate below)*	Only 9% of people consume enough vegetable & fruits to obtain sufficient antioxidants to protect health. These people may benefit from using a complex of carotenoids.	Understandably more expensive than beta carotene. Two capsules once each day.
*Alternate to product #351: **#127 Natural Beta Carotene** (Derived from specially grown and harvested algae.)	• Equivalent to activity of 25,000 IU of vitamin A. Use beta carotene instead of a complex of carotenoids only if you consume a wide variety of vegetables & fruits.	Two capsules once each day.
Vitamin E Occurs naturally in oils (wheat germ, cotton-seed, palm, rice), whole grain cereals, & lettuce.	Also occurs naturally in animal tissue, such as liver, pancreas, heart, muscle, uterus, testes, & blood. Has a wide range of protective effects on the body.	Take with food containing fat or oil.
#71 Natural Vitamin E Complex	• 400 IU (80% d-alpha tocopherol and 20% of other naturally-occurring tocopherols: d-beta d-delta, and d-gamma)	Two-to-four capsules once each day.
Minerals	As important to health as vitamins.	Take with food.
#12 Mineral Insurance Formula		Two tablets two times each day.
• Calcium (Calcium phosphate) (83.4 mg)	• Phosphorus (Calcium phosphate) (83.4 mg)	• Zinc (Gluconate) (5 mg)
• Iron (Ferrous fumarate) (5 mg)	• Magnesium (Oxide) (66.7 mg)	• Iodine (kelp) (50 mcg)
• Copper (gluconate) (0.67 mg)	• Manganese (gluconate) (1.67 mg)	• Molybdenum (amino acid chelate) (33.3 mcg)
• Chromium (amino acid chelate) (66.7 mcg)	• Selenium (sodium selenate) (6.7 mcg)	
Calcium, Magnesium & Vitamin D	For Adults, we recommend roughly 1500 mg of calcium and 750 mg of magnesium per day.	Take with food.
#16 Calcium Complex & Magnesium	(Elemental calcium: 375 mg)	Two tablets two times each day.

(See alternate below)**	• Elemental calcium derived from oyster shell (providing 225 mg calcium)	• Magnesium (oxide) (187 mg)
	• Calcium citrate (providing 25 mg calcium)	• Eggshell (providing 125mg calcium)
Alternate to product #16: **Calcium, Magnesium, & Vitamin D		Two tablets two times each day.
• Elemental calcium, 250 mg derived from calcium carbonate.	• Magnesium, 125 mg (80% from magnesium oxide & 20% from magnesium carbonate.)	• Vitamin D (cholecalciferol) 100 IU
Vitamin C Use one of two options below, either tablets or crystals.	Adjust dose to bowel tolerance.	Important: How to use vitamin C
#47 Vitamin C (ascorbic acid)	• 1,000 mg	One-to-six tablets three times each day.
#84 Vitamin C as Calcium Ascorbate Crystals (See alternate belowค)	Mix with juice or other liquid, or sprinkle on food. One scoopful (scoop provided with order), or ฝ teaspoon, provides approximately:	One -to- six scoops (ฝ teaspoon) three times each day.
	• Vitamin C (approx. 1,000 mg)	• Calcium (approx. 115mg)
คAlternate to product #84: **NutriBiotic's Calcium Ascorbate Cyrstalline Powder**	100% pure buffered vitamin C, pharmaceutical grade. Sold in some health food stores. (NutriBiotic, Lakeport, CA 95453)	• Vitamin C (approx. 1,000 mg) • Calcium (approx. 115 mg)
Fatty Acids Take with food containing fat or oil.	We recommend flax seed oil below for the omega-3 fatty acids in it. Many people are deficient in this fatty acid. Why we recommend omega-3 fatty acids.	Omega-6 deficiency isn't as common, but we list evening primrose oil, which contains it, because it benefits some patients.
#404 Flax Seed Oil 1300 mg of flax seed oil extract. (See alternate below)ฒ	• Contains 740 mg linolenic acid containing alpha-linolenic acid (Omega-3), 208 mg linoleic acid (Omega-6), 234 mg oleic acid (Omega-9).	Two capsules with food each day.
ฒAlternate to product #404: **#116 Super EPA** 500 mg omega-3 fatty acids (marine lipids).	• 300 mg EPA • 200 mg DHA • 1 IU Natural vitamin E	Four capsules with food each day.
#427 Evening Primrose Oil 100% pure cold pressed Evening Primrose Oil.	• Contains 45 mg gamma linolenic acid, 300 mg linoleic acid, & 55 mg oleic acid.	Two capsules with food each day.
If You Have Trouble Swallowing Pills	Use a product such as #353 (see below).	The product should provide amounts of nutrients as close as possible to those we recommend in this table.
#353 All Insurance Vitamin Powder • Contains vitamins, minerals, & amino acids.	You'll need to take several supplements in addition to the powder. These include vitamin C, omega-3 fatty acids, 400 mg calcium, and a Super B tablet.	Two scoops of powder two times each day.v

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Vitamin C Content of Orange Juice

Dr. John C. Lowe

The Journal of the American Dietetic Association (April 2002) recently reported that the vitamin C content of ready-to-drink orange juice products is lower than formerly believed. Four weeks after a container is open, practically all the vitamin C is gone. Compared to frozen juices, ready-to-drink juices have a lower vitamin C content to start with. Ready-to-drink products are put through pasteurization, which destroys some of the vitamin C. When reconstituted, frozen orange juice contains about 86 mg of vitamin C. When a carton of pasteurized juice is opened, it contains only about 45 mg.

I hope, however, that you don't depend on juices for your daily allotment of vitamin C. Optimal health is possible only with amounts of vitamin C that far exceed what juices provide.

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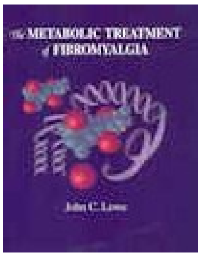

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Why We Recommend Omega-3 Fatty Acids

Dr. John C. Lowe

(Pain-Reducing Effects of Omega-3 Fatty Acids)

We are concerned that our patients achieve optimal health, and for most patients, omega-3 fatty acids are needed for this. We have two reasons for recommending that patients take omega-3 fatty acids. First, some evidence suggests that these fatty acids protect the thyroid gland and may reduce the severity of hypothyroidism. Second, a deficiency of the fatty acids—which is common today—can interfere with normal nervous system and brain function. Among the symptoms that may result are depression and poor memory and concentration. These symptoms are common among hypothyroid and thyroid hormone resistance patients. Providing the patients with adequate thyroid hormone regulation is crucial, of course. But for relieving depression and poor memory and concentration, we can’t overemphasize the importance of patients also correcting an omega-3 fatty acid deficiency.

Need for a Balance of Omega-3 and Omega-6 Fatty Acids. Our human ancestors evolved with a diet that contained about equal amounts of omega-3 and omega-6 fatty acids. (The ratio was about 1-to-1:2.[1]) Over the past 100-to-150 years, humans have increased their intake of vegetable oils from corn, sunflower seeds, safflower seeds, cottonseed, and soybeans. As they did, their intake of omega-6 fatty acids markedly increased.[1] Today, the diets of most people in the West have a high ratio of omega-6 to omega-3 fatty acids. (The ratio ranges from about 20-30:1.[1]) Compared to the diet humans evolved with and with which our genetic patterns developed, the diet is now deficient in omega-3 fatty acids.[1]

A high intake of omega-6 can have adverse effects. The person’s physiologic state shifts so that the blood becomes stickier and bleeding time decreases. Blood vessels constrict more easily and may spasm. In contrast, omega-3 fatty acids oppose inflammation, blood clots, and heart arrhythmias. They also lower blood fats and favor dilation of blood vessels. These effects make omega-3 important in preventing a variety of diseases. These diseases include coronary heart disease, high blood pressure, type-2 diabetes, some forms of kidney disease, rheumatoid arthritis, ulcerative colitis, Crohn's disease, and chronic obstructive pulmonary disease.[1] Some benefits come directly from omega-3 fatty acids. Other benefits come from two other fatty acids that cells derive from omega-3.[1] The two fatty acids are "eicosapentaenoic acid" (EPA) and "docosahexaenoic acid" (DHA).[1][6]

A balance of omega-6 and omega-3 fatty acids in the diet is essential for normal growth and development. Balancing the fatty acids may decrease the incidence of cardiovascular disease and other chronic diseases, and it may improve mental health.[1]

To correct adverse health effects, researches recommend that we decrease the intake of omega-6 fatty acids and increase the intake of omega-3 fatty acids.[1] We can get omega-3 in some foods. The oils of sea fish contain omega-3, but farm-raised, corn-feed fish aren’t a good source. Green leafy vegetables, flaxseed, rapeseed, and walnuts are good sources.[1]

Brain Function. As I said above, our main reason for recommending omega-3 fatty acids is that we want to optimize our patients' brain function. To function normally, the brain must produce several types of fatty acids. To produce them, brain cells must have the required building-block chemicals, such as omega-3.[5] Some fatty acids brain cells produce are important to normal metabolism of brain neurotransmitters. DHA, for example, is involved in dopamine and serotonin metabolism.[6]

Depression occurs more often in people who lower their cholesterol levels through dieting or drugs. The increased incidence of depression with lower cholesterol levels may result from altered levels of fatty acids. The altered levels may involve a deficiency of omega-3 fatty acids or an increase in the ratio of omega-6 to omega-3 fatty acids.[3] Some researchers have reported finding lower omega-3 fatty acid levels in depressed patients. Whether increasing the levels improves depression, however, is still unsettled.[2]

Gitlin, at the Department of Psychiatry at UCLA School of Medicine, reported this year that psychiatrists have expanded the treatment of bipolar disorder. In addition to mood stabilizing drugs, some are also treating their patients with high-dose thyroid hormone and omega-3 fatty acids.[8]

Nutrient deficiencies are common in children with "attention deficit hyperactivity syndrome." Correcting the nutrient deficiencies may improve the childrens' symptoms. Among the nutritional supplements researchers recommend are omega-3 and omega-6 fatty acids. (Other nutrients they recommend include minerals, B complex vitamins, flavonoids, and phospholipid phosphatidylserine.)[7]

Studies have shown that many schizophrenic patients have low levels of the fatty acids needed for normal metabolism of nerve cell membranes. In some studies, evening primrose oil (omega-6) supplementation wasn't of benefit to schizophrenics. But EPA (derived from omega-3) enabled one third of the patients to avoid treatment with anti-psychotic drugs.[4]

These studies typify scores that have recently been published. They illustrate the evidence amassing that a balance of omega-3 and omega-6 fatty acids is important to health in general and to brain function in particular. Omega-3 may be an essential ingredient for relieving some patients' depression and restoring their memory and concentration. Hence, we recommend that patients take it as a daily supplement.

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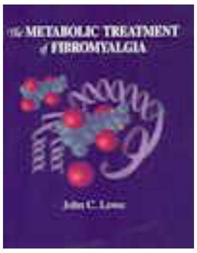

The Metabolic Treatment of Fibromyalgia
by Dr. John C. Lowe
Readers' Comments

Your Guide to Metabolic Health
by Dr. Gina Honeyman-Lowe & Dr. John C. Lowe

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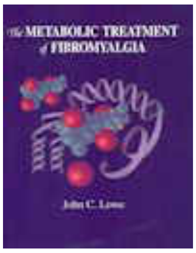

The Metabolic Treatment of Fibromyalgia

Gene Therapy with Coffee and Tea

Dr. John C. Lowe
April 24, 2006

Late this year, I reread Dr. Majid Ali's book *The Canary and Chronic Fatigue*.[1] I had forgotten his emphasis on how, through the decades, we've turned our world into a powerful oxidizing container. Oxidation is a chemical process in which oxygen combines with a substance, changing the substance in some way. Oxidation causes some metals to rust, causes white wine to darken and lose its freshness, and damages cell membranes and ages skin.

Dr. Ali's main hypothesis in the book is that excess oxidation is a major cause of health problems such as chronic fatigue. Since he wrote the book, many studies have vindicated his hypothesis. The published research literature is massive. It's so vast that rather than citing references here, we encourage our readers to go to PubMed and search for key terms such as "oxidation," "oxidative stress," "chronic fatigue," and "disease."

The Bush administration has rolled back many regulations that had improved the quality of our environment. The regulations had reduced oxidative damage. By unleashing industry to pollute as it hadn't in decades, the administration has vastly worsened the potential oxidative damage to us all. It's good for business, as George W. Bush often says. But, as Dr. Ali noted, it's dreadfully bad for our health.

I often point out that unless people with a sustainability consciousness come to set and implement environmental policies, our environment isn't going to be cleaned up. Even if we made a turn about today, it would take time for the earth to heal. We have to adapt to the current level of pollution and find ways to be healthy in spite of them. The chemical contaminants that saturate us all are going to continue to do so, and the oxidizing power of our environment is most likely going to worsen.

Adapting to a highly oxidizing environment means augmenting our ability to counter the oxidation—that is, building our antioxidant power. One way we can do this is to drink organic tea and coffee every day.

Trevisanato and Kim described the health benefits of tea after reviewing the research literature: "Tea contains biologically active compounds that help prevent a wide variety of diseases. A growing body of evidence suggests that moderate consumption of tea may protect against several forms of cancer, cardiovascular diseases, the formation of kidney stones, bacterial infections, and dental cavities."[2]

Tea contains many beneficial chemical compounds, including vitamins and fluoride (although we should avoid excess fluoride). Tea is the richest source of a class of antioxidants called "flavonoids," and green and black teas contain large amounts of other powerful antioxidants called "catechins" and "polyphenols."[2][3]

Plant polyphenols are *potent* antioxidant compounds. Some researchers

by Dr. John C. Lowe
Readers' Comments

consider them the main agents in fruits, vegetables, and red wines that protect us from oxidative stress.[9] Regularly eating plant foods and drinking beverages laden with polyphenols is actually a form of gene therapy. Polyphenols increase the activity of the gene that codes for "glutathione." Glutathione is the body's most widespread and powerful antioxidant. By drinking green or black tea often enough, we increase gene transcription for glutathione. Our cells then use that transcribed genetic code to increase our cells' production of glutathione. The increased glutathione in our cells then protects us from harmful oxidation.

Tea isn't the only beverage that contains large amounts of polyphenols. Elderberry juice contains huge amounts.[4] This may be why elderberry extract, which we always keep on hand, is so effective in short circuiting viral infections. Both red wines and prunes contain large amounts of polyphenols. Fruit juice and vegetable juice contain considerable but less amounts. And dark and lager beers and white wines contain even less.[4]

Polyphenols in coffee markedly increase our antioxidant capacity.[5] The Agriculture Department writes that the typical adult American drinks 1.64 cups of coffee each day. Chemist Dr. Joe Vinson calculated that coffee provides a *huge* load of antioxidants compared to other beverages. To illustrate, an amount of tea equivalent to the 1.64 cups of coffee provided 294 milligrams of antioxidants. By comparison, the coffee provided 1,299 milligrams.[6]

Organic coffee and tea are a daily part of our health regimen, and we encourage others to consider including them in theirs. If you don't do well on caffeine, you can take in large amounts of polyphenols through decaffeinated coffee and tea. Decaffeinating beverages doesn't remove these powerful health protectors.[7][8]

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Four 2003 Studies of Thyroid Hormone Replacement Therapies: Logical Analysis and Ethical Implications

by Dr. John C. Lowe
Diplomate: American Academy of Pain Management
Director of Research: Fibromyalgia Research Foundation
1007 Pearl Street, Suite 280, Boulder, CO, 80302 USA
DrJohnLowe@aol.com

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May 4, 2004

Abstract. "Replacement" is the most widely used approach to thyroid hormone therapy. Clinical practice guidelines define replacement therapy as: adjustment of a patient’s thyroid hormone dosage so that his or her TSH and thyroid hormone levels remain within current laboratory reference ranges. Overall, the endocrinology specialty endorses T4-replacement as the preferable approach to thyroid hormone therapy.

Four studies published in late 2003 compared the effectiveness of two types of replacement therapy, T4 alone and combined T4 and T3 (T4/T3). In three of the studies,[1][2][3] patients who took part had been suffering from hypothyroid symptoms despite their T4-replacement therapy. The studies showed that neither form of replacement therapy improved the patients’ symptoms. In the fourth study,[4] researchers gave psychometric tests to hypothyroid infants after they had been on either T4- or T4/T3-replacement therapy for six and then twelve months. Compared to healthy infants, hypothyroid infants on both types of replacement therapy had impaired psychomotor function.

In reporting this specific result of the studies—that neither type of *replacement therapy* effectively relieved patients’ symptoms or abnormal neuropsychological test results—three groups of people have misrepresented, perhaps inadvertently, the outcome: the endocrinology researchers who conducted the studies, the endocrinologists who commented on them, and the journalists who reported them. Rather than reporting the specific study result, these groups reported a false general conclusion: that no approach to T4/T3 therapy (replacement is the only one they tested) was more effective than T4 alone. This false general conclusion violates a rule of quality scientific reporting—that we precisely formulate our statements to accurately convey conclusions that we can validly deduce from the studies we report.

Oddly, based on the negative outcome of these studies, some endocrinologists advise that T4-replacement should remain the treatment of choice for hypothyroid

patients. Their advice, however, disregards two humanitarian imperatives:

> (1) The endocrinology specialty must officially and publicly concede that many patients continue to suffer from hypothyroid symptoms despite their use of replacement therapies. This is especially important in view of other studies. The other studies suggest that for many patients, T4-replacement therapy increases the incidence of potentially fatal diseases and boosts chronic drug use to control the patients' hypothyroid symptoms and those of the other diseases.
>
> (2) These patients must have access to alternate thyroid hormone therapies, especially TSH-suppressive therapies, that are safe and effective for them.

These imperatives require that the endocrinology specialty now impartially consider approaches to thyroid hormone therapy other than replacement.

Alternate thyroid hormone therapies are already in demand and in widespread use by hypothyroid patients for whom T4-replacement is ineffective. These patients, many clinicians, and some researchers report that the alternate therapies are far more effective for the patients than replacement therapies. The endocrinology specialty's objections to these other therapies have been either speculative or based on invalid conclusions from studies.

This imposes an urgent scientific obligation on the endocrinology specialty: that it now open-mindedly reevaluate its objections to alternate thyroid hormone therapies. This is essential on both humanitarian and ethical grounds. In light of this obligation, endocrinology researchers must now cooperate in comparing the safety and effectiveness of replacement therapies to the alternate therapies. They must do this by reassessing without prejudice the already available historical, scientific, and clinical evidence; and by then conducting new, well-designed comparative studies.

The endocrinology specialty faces a dilemma in considering a reassessment of its objections to alternate thyroid hormone therapies. It will find that it can best serve the welfare of hypothyroid patients for whom T4-replacement is ineffective by providing them with alternate thyroid hormone therapies. But, by providing other therapies for these patients, the specialty will risk losing financial support from the corporations that profit from its endorsement of T4-replacement. The result for the endocrinology specialty is that it will be compelled to show a steadfast commitment to scientific truth and patient welfare, or risk being deemed corrupt.

In this critique, I explain my statements in this abstract. I also provide supporting evidence for my conclusions.

False Reports of 2003 Study Results and Potential Problems From Them

In 2003, four studies were published that compared the effectiveness of two types of replacement therapy, T4 alone and combined T4/T3, in the treatment of hypothyroid patients. In one study, symptoms of patients taking either T4-replacement or T4/T3-replacement improved.[3] Because both groups improved, for logical reasons we must attribute the improvement to either a placebo effect[20] or a natural variation in the patients' symptoms. Essentially, then, in this study as in the other three, neither type of replacement therapy improved the patients' symptoms or test abnormalities.[1][2][3][4] Therefore, the conclusion compelled by the outcome of the four studies is clear:

> Replacement therapies are ineffective for many hypothyroid patients, leaving them symptomatic and with some abnormal neuropsychological test results.

Based on the four studies, endocrinologists have advised that T4-replacement should remain the treatment of choice for hypothyroid patients. Their reason is that T4/T3-replacement worked no better than T4-replacement. This advice is foreboding for patients who remain symptomatic on T4-replacement, for the four studies are a concession of endocrinology researchers that the therapy leaves many patients suffering. For these patients' welfare, endocrinologists are obligated to reassess their advice in view of its predictable pernicious consequences for the patients. I explain this in the section below titled "Dilemma for the Endocrinology Specialty."

First, however, I'll point out an invalid conclusion endocrinologists stated in their reports of the study results. Patients, physicians, reporters, and the endocrinologists themselves must understand the invalidity of the conclusion; otherwise, they are likely to promulgate a false belief about the results of the studies.

Valid and Invalid Conclusions of the Endocrinology Researchers, Commentators, and Journalists

The researchers accomplished what they intended in each of the four studies. They tested the relative effectiveness of *two types of replacement therapy;* they found that neither type improved patients' hypothyroid symptoms. Endocrinologists' reports of the results contain the valid conclusion that neither type improved patients' symptoms. Unfortunately, the reports also contain an invalid conclusion, one that we clearly cannot deduce from the study results.

> The invalid conclusion is that no approach to T4/T3 therapy—among all possible approaches—is any more effective than T4 alone.

This invalid conclusion is a linguistic reformulation of the valid one. I'll explain this in the lexicon of the logician. The endocrinologists deduced from the studies a valid existential (specific) proposition: Neither *T4-replacement nor T4/T3-replacement* improved patients' hypothyroid symptoms. Then, they reformulated that proposition into an invalid universal (all-inclusive) proposition: No approach to T4/T3 therapy is more effective than T4 alone in relieving patients' hypothyroid symptoms.

These differently formulated conclusions have entirely different meanings. The difference is the same as researchers first saying, "Our study showed that as race horses, *short* stallions are no more effective than *short* mares," and then concluding, ". . . as race horses, stallions are no more effective than mares." The first statement refers to a specific class of stallions and mares—short ones; the second refers to *all* stallions and *all* mares, despite their height. In that the researchers studied only short stallions and mares—not all stallions and mares—they cannot validly deduce their second proposition from the first. To do so is a flagrant *non sequitur*.

The endocrinologists who performed these studies committed exactly the same logical error and reported an equally flagrant *non sequitur*. They cannot validly deduce from the results of the four studies that no T4/T3 therapy works any better than T4 alone; yet this is precisely the meaning of their universal conclusion (and the implication of the titles of all four study reports).[1][2][3][4]

The endocrinologists may have reformulated their valid conclusion into an invalid one inadvertently. But that doesn't change the fact that their doing so violates a rule of quality scientific reporting—that we *precisely* formulate our statements to accurately convey *only* the valid conclusions deducible from study results.

In Addendum 1, I've excerpted statements from the endocrinologists' published reports of the studies. The excerpts show that each of the published reports contains both valid and invalid conclusions.

In response to my distinction between the valid and invalid conclusions, I predict a particular protest: I'm quibbling; what I'm referring to as an invalid conclusion is only a version of the conclusion abridged to be wieldy and understandable—an abridgment demanded by journal and newspaper editors. But to abridge is to shorten while maintaining the basic meaning—not to convert a valid specific statement into an invalid universal one.

It is understandable that reporters and editors of newspapers and newsletters sometimes fail to accurately report conclusions from studies. Most aren't practicing researchers, and we can excuse them for occasionally lacking the precision expected of researchers. To understand their imprecision, however, is not to condone it; we should implore them to accurately report the results of scientific studies. In this case, however, reporters and editors are only parroting an invalid conclusion from the researchers themselves.

Endocrinologists have perpetuated other invalid and false conclusions (see section below titled "Potential Harm from TSH-Suppressive Dosages of Thyroid Hormone") that reporters have parroted. It would be inexcusable, however, to have to add to the list the invalid conclusion now at issue.

Few physicians, patients, or reporters will read the full-text reports of the four studies. Instead, they'll read only the brief invalid conclusion of the researchers in various publications. Some will read only the abstracts of the four reports in *PubMed*. As a result, it's likely that they'll falsely believe the researchers found that no approach to T4/T3 therapy is more effective than T4 alone.

Already in *JAMA*, we see the title of an article, "Combined T4 and T3 Therapy—Back to the Drawing Board."[20] In that this title is not properly qualified, many doctors, fast-moving by necessity, will read only the headline, and their belief system will inaccurately echo it. No more Armour or Thyrolar for their patients! After all, the doctors have an ethical obligation to go where science points. Armour and Thyrolar contain T4 and T3. The studies show that these are no more effective than T4 alone, so the doctors must prescribe T4 alone, as the researchers advise.

Few reporters who read the researchers' full reports or abstracts of them are likely to announce to their readers what the researchers actually found. Instead, they'll quote or rephrase what they read in the reports or abstracts—the invalid conclusion. To illustrate, the invalid conclusion of the endocrinology researchers and commentators was the headline of a news article at a popular website, docguide.com: "Combination Levothyroxine/Liothyronine [T4/T3] Shows No Obvious Benefit Over Levothyroxine [T4] Alone in Patients With Primary Hypothyroidism." The first sentence of the article echoed the title: "Patients who are treated with a combination of levothyroxine plus liothyronine for primary hypothyroidism gained no apparent benefit compared with patients treated with levothyroxine monotherapy, say researchers."[21] The headline alone is certain to mislead readers who stop there. The intention of the reporter, Joene Hendry, most likely was not to mislead. But in abbreviating the studies' conclusion, that is exactly, though inadvertently, what she did.

Hence, a false belief about T4/T3 therapies has already been engendered by endocrinologists' violation of this rule of quality science reporting. Researchers, physicians, patients, and reporters should exhort the endocrinologists to practice the same precision that we implore reporters to practice. Whether the endocrinologists heed the exhortation is a matter of scientific integrity.

Endocrinologists' Odd Treatment Advice for Patients Who Remain Symptomatic on T4-replacement Therapy

The four studies showed that replacement therapies weren't effective for many hypothyroid patients.[1][2][3][4] Patients who took part in three of the studies had hypothyroid symptoms and/or abnormal neuropsychological test scores. T4-replacement therapy clearly didn't improve the symptoms or the scores. Regardless, the researchers and other endocrinologists have since implicitly or explicitly given baffling advice based on the studies: that T4-replacement should remain the treatment of choice for hypothyroid patients.[1][2][3][19] (For quotes from endocrinologists to this effect, see Addendum 2.)

This is the equivalent of researchers taking people who suffer from thirst when restricted to one glass of water per day; letting them try as an alternative one glass of mixed water and tea; seeing that the one-glass mixture relieves thirst no better than one glass of water; and then, based on this outcome, advising that these people continue to drink one glass of water per day. The one glass of water left the people thirsty before the study, and failure of the one-glass mixture to relieve their thirst doesn't mean one glass of water alone will now do any better than before. Similarly, many hypothyroid patients have continuing symptoms on T4-replacement, and the failure of T4/T3-replacement to relieve their symptoms doesn't mean that now T4-replacement will.

As the endocrinologists imply, T4-replacement (and T4/T3-replacement, which they discourage) will indeed work well for *some* hypothyroid patients. For others, however, replacement therapies are clearly ineffective. The studies are in fact "a randomized double-blind" admission by the endocrinology researchers that T4-replacement is not effective for many patients. (See Addendum 3 for evidence of persisting symptoms of hypothyroid patients in the studies despite their use of T4-replacement.)

Despite this, none of the endocrinologists have noted an ethical and humanitarian responsibility made clear by these studies: to provide patients for whom replacement therapies aren't effective with alternate thyroid hormone therapies that are safe and effective for them. This responsibility is made even clearer by several other studies. These studies indicate that patients on T4-replacement have an increased incidence of potentially fatal diseases, and increased chronic use of medications for these diseases (see section below titled "Presumptions of the Endocrinology Specialty: Instability of Desiccated Thyroid, Dangers of T3, and the Safety and Effectiveness of T4-replacement"). The endocrinologists' failure to note this responsibility suggests a cavalier disregard for the needs of patients who remain symptomatic and susceptible to pathology on T4-replacement therapy. The only humane option for the endocrinology specialty is to now open-mindedly reconsider thyroid hormone therapies other than replacement, including TSH-suppressive therapies.

Alternate Approaches to Thyroid Hormone Therapy

Thyroid hormone treatments other than replacement therapies are in widespread use among hypothyroid patients—mainly those who previously failed to benefit, or benefit enough, from T4-replacement. The therapies are in widespread use for one reason: they work for hypothyroid patients after replacement therapies failed them.

The most effective of these therapies involves adjusting patients' dosages of combined T4/T3 or T3 alone according to several indices other than TSH and thyroid hormone levels. Those indices are signs, symptoms, and various objective measures of tissue response to particular dosages. When patients' dosages are titrated according to these indices, dosages that prove safe and effective are typically TSH-suppressive.[44] Evidence is available that this therapeutic approach relieves patients' signs, symptoms, and measurable tissue abnormalities such as low resting metabolic rates (RMR) according to indirect calorimetry.

In the studies at issue, endocrinologists used thyroid function test results as the exclusive criteria by which to titrate patients' thyroid hormone dosages. Despite denials,[26] this is precisely the method used by endocrinologists at large to titrate patients' dosages. This method (which I termed "extremist medical technocracy" in *The Metabolic of Treatment Fibromyalgia*[44]) varies from that of the clinician using the protocol I describe here. This clinician uses thyroid function test results as an aid to clinical judgment—an aid that is integrated with other aids, such as objective measures of tissue response to thyroid hormone. Thyroid function test results help this clinician form an opinion as to the patient's pre-treatment thyroid status. After he establishes the patient's thyroid status, however, he seldom uses thyroid function test results to reach treatment decisions. His reason for not using them to titrate dosage is that most of his patients have previously failed to benefit from T4- or T4/T3-replacement therapies, in which, of course, physicians adjusted dosages according to the patients' TSH and/or thyroid hormone levels. Only by this clinician not using the replacement method for titrating dosage are most of these patients able to recover from their symptoms, signs, and objective measures of tissue hypometabolism.

The fact that so many patients have recovered from their symptoms, signs, and tissue abnormalities with this alternative to replacement therapies compels a proposition: T4-replacement therapy previously impeded these patients from recovering their health. It becomes imperative, then, for the health and welfare of such patients that practitioners

> (1) not restrict them to replacement therapies, but instead,
>
> (2) permit them to undergo trials of alternate thyroid hormone therapies, and
>
> (3) determine on an individual basis, using clinical indicators and objective measures of tissue responses, whether the alternate therapies are safe and effective for each individual patient.

Despite this clear-cut imperative, Kaplan et al., in their editorial comments on the four studies, stipulated that in future studies, "TSH should be monitored dynamically and study medications adjusted according to the results, to maintain normal serum TSH concentrations."[19,p.4541] To make this recommendation, Kaplan et al. had to ignore the major finding of the four studies: that replacement therapies—in which clinicians adjust patients' dosages to maintain reference range TSH levels—are ineffective for many hypothyroid patients (and specifically for most patients in the four studies), leaving them to suffer from hypothyroid symptoms.

In their editorial, Kaplan et al. also appear to ignore a telling observation of their own: in one study, 15 thyroid cancer patients used TSH-suppressive dosages of thyroid hormone; their mood and cognitive function improved more than those of patients with autoimmune thyroiditis who used replacement dosages.[19,p.4540] This observation suggests that dosages higher than those dictated by the replacement concept more effectively relieve patients' hypothyroid symptoms. Other research has shown that patients report feeling better with TSH-suppressive dosages of thyroid hormone.[23][24][25] Moreover, psychiatrists report that dosages of T3 higher than replacement dosages augment the depression-relieving effects of antidepressants.[9][28][29][30][31][34] In addition, in a study of patients made hypothyroid by therapeutic destruction of the thyroid gland, some used TSH-suppressive dosages of thyroid hormone and others used T4-replacement. Those on TSH-suppressive dosages didn't gain excess weight; those on T4-replacement did. The researchers concluded that T4-replacement was the cause of the excess weight gain.[55] These published reports are consistent with thousands of cases in which hypothyroid patients recovered from their symptoms and other health problems with TSH-suppressive dosages of thyroid hormone *after* T4-replacement failed to help them.

Kaplan's observation also suggests another point: that T4-replacement keeps many hypothyroid patients' dosages too low to relieve their symptoms is an indictment of the concept of replacement. As the cause of

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T4-replacement constitutes a public health menace—one responsible for colossal human suffering and huge financial burden to society.

In view of this circumstance, the advice of Kaplan et al. appears to be indefensible. It also appears, based on the outcome of the four studies, that the endocrinology specialty now has an ethical and humanitarian obligation to challenge the veracity of its own presumptions about the safety and effectiveness of replacement therapies. (See section below titled "Presumptions of the Endocrinology Specialty:

Instability of Desiccated Thyroid, Dangers of T3, and the Safety and Effectiveness of T4-replacement.")

As I wrote above, alternate thyroid hormone therapies are already in widespread use, and physicians and patients who use them contend that treatment results are superior to those of T4-replacement. These reports, in light of the outcome of the four studies, should impel anyone even mildly charitable toward patients who suffer while on T4-replacement, to advocate studies comparing T4-replacement with alternate thyroid hormone therapies.

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I anticipate an objection of the endocrinology specialty to my behest that it consider without prejudice the need of many patients for TSH-suppressive thyroid hormone therapies. The specialty's reason for objecting to such therapies has long been the issue of patient safety. The specialty as a whole tenaciously argues that TSH-suppressive dosages of thyroid hormone imperil patients, risking bone demineralization, acute adrenal crisis, and atrial fibrillation.

In Addendum 4, I provide a brief summary of each of these putative adverse effects. Each is either speculative, never shown to be clinically significant, or based on invalid deductions from studies.

The specialty has argued that T4-replacement therapy is superior to other approaches to thyroid hormone therapy because it enables patients' TSH and thyroid hormone levels to remain stably within their reference ranges. The idea that stability within the reference ranges is vital to the safety of all patients, however, is a presumption. Studies show that keeping these hormones within their reference ranges harms many patients in three ways: it perpetuates their hypothyroid symptoms, increases the incidence of potentially fatal diseases, and increases patients' regular use of drugs to control their hypothyroid symptoms and the other diseases.

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Four 2003 Studies of Thyroid Hormone Replacement Therapies: Logical Analysis and Ethical Implications

by Dr. John C. Lowe
Diplomate: American Academy of Pain Management
Director of Research: Fibromyalgia Research Foundation
1007 Pearl Street, Suite 280, Boulder, CO, 80302 USA
DrJohnLowe@aol.com

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May 4, 2004

Abstract. "Replacement" is the most widely used approach to thyroid hormone therapy. Clinical practice guidelines define replacement therapy as: adjustment of a patient's thyroid hormone dosage so that his or her TSH and thyroid hormone levels remain within current laboratory reference ranges. Overall, the endocrinology specialty endorses T4-replacement as the preferable approach to thyroid hormone therapy.

Four studies published in late 2003 compared the effectiveness of two types of replacement therapy, T4 alone and combined T4 and T3 (T4/T3). In three of the studies,[1][2][3] patients who took part had been suffering from hypothyroid symptoms despite their T4-replacement therapy. The studies showed that neither form of replacement therapy improved the patients' symptoms. In the fourth study,[4] researchers gave psychometric tests to hypothyroid infants after they had been on either T4- or T4/T3-replacement therapy for six and then twelve months. Compared to healthy infants, hypothyroid infants on both types of replacement therapy had impaired psychomotor function.

In reporting this specific result of the studies—that neither type of *replacement therapy* effectively relieved patients' symptoms or abnormal neuropsychological test results—three groups of people have misrepresented, perhaps inadvertently, the outcome: the endocrinology researchers who conducted the studies, the endocrinologists who commented on them, and the journalists who reported them. Rather than reporting the specific study result, these groups reported a false general conclusion: that no approach to T4/T3 therapy (replacement is the only one they tested) was more effective than T4 alone. This false general conclusion violates a rule of quality scientific reporting—that we precisely formulate our statements to accurately convey conclusions that we can validly deduce from the studies we report.

Oddly, based on the negative outcome of these studies, some endocrinologists advise that T4-replacement should remain the treatment of choice for hypothyroid

patients. Their advice, however, disregards two humanitarian imperatives:

> (1) The endocrinology specialty must officially and publicly concede that many patients continue to suffer from hypothyroid symptoms despite their use of replacement therapies. This is especially important in view of other studies. The other studies suggest that for many patients, T4-replacement therapy increases the incidence of potentially fatal diseases and boosts chronic drug use to control the patients' hypothyroid symptoms and those of the other diseases.
>
> (2) These patients must have access to alternate thyroid hormone therapies, especially TSH-suppressive therapies, that are safe and effective for them.

These imperatives require that the endocrinology specialty now impartially consider approaches to thyroid hormone therapy other than replacement.

Alternate thyroid hormone therapies are already in demand and in widespread use by hypothyroid patients for whom T4-replacement is ineffective. These patients, many clinicians, and some researchers report that the alternate therapies are far more effective for the patients than replacement therapies. The endocrinology specialty's objections to these other therapies have been either speculative or based on invalid conclusions from studies.

This imposes an urgent scientific obligation on the endocrinology specialty: that it now open-mindedly reevaluate its objections to alternate thyroid hormone therapies. This is essential on both humanitarian and ethical grounds. In light of this obligation, endocrinology researchers must now cooperate in comparing the safety and effectiveness of replacement therapies to the alternate therapies. They must do this by reassessing without prejudice the already available historical, scientific, and clinical evidence; and by then conducting new, well-designed comparative studies.

The endocrinology specialty faces a dilemma in considering a reassessment of its objections to alternate thyroid hormone therapies. It will find that it can best serve the welfare of hypothyroid patients for whom T4-replacement is ineffective by providing them with alternate thyroid hormone therapies. But, by providing other therapies for these patients, the specialty will risk losing financial support from the corporations that profit from its endorsement of T4-replacement. The result for the endocrinology specialty is that it will be compelled to show a steadfast commitment to scientific truth and patient welfare, or risk being deemed corrupt.

In this critique, I explain my statements in this abstract. I also provide supporting evidence for my conclusions.

False Reports of 2003 Study Results and Potential Problems From Them

In 2003, four studies were published that compared the effectiveness of two types of replacement therapy, T4 alone and combined T4/T3, in the treatment of hypothyroid patients. In one study, symptoms of patients taking either T4-replacement or T4/T3-replacement improved.[3] Because both groups improved, for logical reasons we must attribute the improvement to either a placebo effect[20] or a natural variation in the patients' symptoms. Essentially, then, in this study as in the other three, neither type of replacement therapy improved the patients' symptoms or test abnormalities.[1][2][3][4] Therefore, the conclusion compelled by the outcome of the four studies is clear:

> Replacement therapies are ineffective for many hypothyroid patients, leaving them symptomatic and with some abnormal neuropsychological test results.

Based on the four studies, endocrinologists have advised that T4-replacement should remain the treatment of choice for hypothyroid patients. Their reason is that T4/T3-replacement worked no better than T4-replacement. This advice is foreboding for patients who remain symptomatic on T4-replacement, for the four studies are a concession of endocrinology researchers that the therapy leaves many patients suffering. For these patients' welfare, endocrinologists are obligated to reassess their advice in view of its predictable pernicious consequences for the patients. I explain this in the section below titled "Dilemma for the Endocrinology Specialty."

First, however, I'll point out an invalid conclusion endocrinologists stated in their reports of the study results. Patients, physicians, reporters, and the endocrinologists themselves must understand the invalidity of the conclusion; otherwise, they are likely to promulgate a false belief about the results of the studies.

Valid and Invalid Conclusions of the Endocrinology Researchers, Commentators, and Journalists

The researchers accomplished what they intended in each of the four studies. They tested the relative effectiveness of *two types of replacement therapy;* they found that neither type improved patients' hypothyroid symptoms. Endocrinologists' reports of the results contain the valid conclusion that neither type improved patients' symptoms. Unfortunately, the reports also contain an invalid conclusion, one that we clearly cannot deduce from the study results.

> The invalid conclusion is that no approach to T4/T3 therapy—among all possible approaches—is any more effective than T4 alone.

This invalid conclusion is a linguistic reformulation of the valid one. I'll explain this in the lexicon of the logician. The endocrinologists deduced from the studies a valid existential (specific) proposition: Neither *T4-replacement nor T4/T3-replacement* improved patients' hypothyroid symptoms. Then, they reformulated that proposition into an invalid universal (all-inclusive) proposition: No approach to T4/T3 therapy is more effective than T4 alone in relieving patients' hypothyroid symptoms.

These differently formulated conclusions have entirely different meanings. The difference is the same as researchers first saying, "Our study showed that as race horses, *short* stallions are no more effective than *short* mares," and then concluding, ". . . as race horses, stallions are no more effective than mares." The first statement refers to a specific class of stallions and mares—short ones; the second refers to *all* stallions and *all* mares, despite their height. In that the researchers studied only short stallions and mares—not all stallions and mares—they cannot validly deduce their second proposition from the first. To do so is a flagrant *non sequitur*.

The endocrinologists who performed these studies committed exactly the same logical error and reported an equally flagrant *non sequitur*. They cannot validly deduce from the results of the four studies that no T4/T3 therapy works any better than T4 alone; yet this is precisely the meaning of their universal conclusion (and the implication of the titles of all four study reports).[1][2][3][4]

The endocrinologists may have reformulated their valid conclusion into an invalid one inadvertently. But that doesn't change the fact that their doing so violates a rule of quality scientific reporting—that we *precisely* formulate our statements to accurately convey *only* the valid conclusions deducible from study results.

In Addendum 1, I've excerpted statements from the endocrinologists' published reports of the studies. The excerpts show that each of the published reports contains both valid and invalid conclusions.

In response to my distinction between the valid and invalid conclusions, I predict a particular protest: I'm quibbling; what I'm referring to as an invalid conclusion is only a version of the conclusion abridged to be wieldy and understandable—an abridgment demanded by journal and newspaper editors. But to abridge is to shorten while maintaining the basic meaning—not to convert a valid specific statement into an invalid universal one.

It is understandable that reporters and editors of newspapers and newsletters sometimes fail to accurately report conclusions from studies. Most aren't practicing researchers, and we can excuse them for occasionally lacking the precision expected of researchers. To understand their imprecision, however, is not to condone it; we should implore them to accurately report the results of scientific studies. In this case, however, reporters and editors are only parroting an invalid conclusion from the researchers themselves.

Endocrinologists have perpetuated other invalid and false conclusions (see section below titled "Potential Harm from TSH-Suppressive Dosages of Thyroid Hormone") that reporters have parroted. It would be inexcusable, however, to have to add to the list the invalid conclusion now at issue.

Few physicians, patients, or reporters will read the full-text reports of the four studies. Instead, they'll read only the brief invalid conclusion of the researchers in various publications. Some will read only the abstracts of the four reports in *PubMed*. As a result, it's likely that they'll falsely believe the researchers found that no approach to T4/T3 therapy is more effective than T4 alone.

Already in *JAMA*, we see the title of an article, "Combined T4 and T3 Therapy—Back to the Drawing Board."[20] In that this title is not properly qualified, many doctors, fast-moving by necessity, will read only the headline, and their belief system will inaccurately echo it. No more Armour or Thyrolar for their patients! After all, the doctors have an ethical obligation to go where science points. Armour and Thyrolar contain T4 and T3. The studies show that these are no more effective than T4 alone, so the doctors must prescribe T4 alone, as the researchers advise.

Few reporters who read the researchers' full reports or abstracts of them are likely to announce to their readers what the researchers actually found. Instead, they'll quote or rephrase what they read in the reports or abstracts—the invalid conclusion. To illustrate, the invalid conclusion of the endocrinology researchers and commentators was the headline of a news article at a popular website, docguide.com: "Combination Levothyroxine/Liothyronine [T4/T3] Shows No Obvious Benefit Over Levothyroxine [T4] Alone in Patients With Primary Hypothyroidism." The first sentence of the article echoed the title: "Patients who are treated with a combination of levothyroxine plus liothyronine for primary hypothyroidism gained no apparent benefit compared with patients treated with levothyroxine monotherapy, say researchers."[21] The headline alone is certain to mislead readers who stop there. The intention of the reporter, Joene Hendry, most likely was not to mislead. But in abbreviating the studies' conclusion, that is exactly, though inadvertently, what she did.

Hence, a false belief about T4/T3 therapies has already been engendered by endocrinologists' violation of this rule of quality science reporting. Researchers, physicians, patients, and reporters should exhort the endocrinologists to practice the same precision that we implore reporters to practice. Whether the endocrinologists heed the exhortation is a matter of scientific integrity.

Endocrinologists' Odd Treatment Advice for Patients Who Remain Symptomatic on T4-replacement Therapy

The four studies showed that replacement therapies weren't effective for many hypothyroid patients.[1][2][3][4] Patients who took part in three of the studies had hypothyroid symptoms and/or abnormal neuropsychological test scores. T4-replacement therapy clearly didn't improve the symptoms or the scores. Regardless, the researchers and other endocrinologists have since implicitly or explicitly given baffling advice based on the studies: that T4-replacement should remain the treatment of choice for hypothyroid patients.[1][2][3][19] (For quotes from endocrinologists to this effect, see Addendum 2.)

This is the equivalent of researchers taking people who suffer from thirst when restricted to one glass of water per day; letting them try as an alternative one glass of mixed water and tea; seeing that the one-glass mixture relieves thirst no better than one glass of water; and then, based on this outcome, advising that these people continue to drink one glass of water per day. The one glass of water left the people thirsty before the study, and failure of the one-glass mixture to relieve their thirst doesn't mean one glass of water alone will now do any better than before. Similarly, many hypothyroid patients have continuing symptoms on T4-replacement, and the failure of T4/T3-replacement to relieve their symptoms doesn't mean that now T4-replacement will.

As the endocrinologists imply, T4-replacement (and T4/T3-replacement, which they discourage) will indeed work well for *some* hypothyroid patients. For others, however, replacement therapies are clearly ineffective. The studies are in fact "a randomized double-blind" admission by the endocrinology researchers that T4-replacement is not effective for many patients. (See Addendum 3 for evidence of persisting symptoms of hypothyroid patients in the studies despite their use of T4-replacement.)

Despite this, none of the endocrinologists have noted an ethical and humanitarian responsibility made clear by these studies: to provide patients for whom replacement therapies aren't effective with alternate thyroid hormone therapies that are safe and effective for them. This responsibility is made even clearer by several other studies. These studies indicate that patients on T4-replacement have an increased incidence of potentially fatal diseases, and increased chronic use of medications for these diseases (see section below titled "Presumptions of the Endocrinology Specialty: Instability of Desiccated Thyroid, Dangers of T3, and the Safety and Effectiveness of T4-replacement"). The endocrinologists' failure to note this responsibility suggests a cavalier disregard for the needs of patients who remain symptomatic and susceptible to pathology on T4-replacement therapy. The only humane option for the endocrinology specialty is to now open-mindedly reconsider thyroid hormone therapies other than replacement, including TSH-suppressive therapies.

Alternate Approaches to Thyroid Hormone Therapy

Thyroid hormone treatments other than replacement therapies are in widespread use among hypothyroid patients—mainly those who previously failed to benefit, or benefit enough, from T4-replacement. The therapies are in widespread use for one reason: they work for hypothyroid patients after replacement therapies failed them.

The most effective of these therapies involves adjusting patients' dosages of combined T4/T3 or T3 alone according to several indices other than TSH and thyroid hormone levels. Those indices are signs, symptoms, and various objective measures of tissue response to particular dosages. When patients' dosages are titrated according to these indices, dosages that prove safe and effective are typically TSH-suppressive.[44] Evidence is available that this therapeutic approach relieves patients' signs, symptoms, and measurable tissue abnormalities such as low resting metabolic rates (RMR) according to indirect calorimetry.

In the studies at issue, endocrinologists used thyroid function test results as the exclusive criteria by which to titrate patients' thyroid hormone dosages. Despite denials,[26] this is precisely the method used by endocrinologists at large to titrate patients' dosages. This method (which I termed "extremist medical technocracy" in *The Metabolic of Treatment Fibromyalgia*[44]) varies from that of the clinician using the protocol I describe here. This clinician uses thyroid function test results as an aid to clinical judgment—an aid that is integrated with other aids, such as objective measures of tissue response to thyroid hormone. Thyroid function test results help this clinician form an opinion as to the patient's pre-treatment thyroid status. After he establishes the patient's thyroid status, however, he seldom uses thyroid function test results to reach treatment decisions. His reason for not using them to titrate dosage is that most of his patients have previously failed to benefit from T4- or T4/T3-replacement therapies, in which, of course, physicians adjusted dosages according to the patients' TSH and/or thyroid hormone levels. Only by this clinician not using the replacement method for titrating dosage are most of these patients able to recover from their symptoms, signs, and objective measures of tissue hypometabolism.

The fact that so many patients have recovered from their symptoms, signs, and tissue abnormalities with this alternative to replacement therapies compels a proposition: T4-replacement therapy previously impeded these patients from recovering their health. It becomes imperative, then, for the health and welfare of such patients that practitioners

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>
> (2) permit them to undergo trials of alternate thyroid hormone therapies, and
>
> (3) determine on an individual basis, using clinical indicators and objective measures of tissue responses, whether the alternate therapies are safe and effective for each individual patient.

Despite this clear-cut imperative, Kaplan et al., in their editorial comments on the four studies, stipulated that in future studies, "TSH should be monitored dynamically and study medications adjusted according to the results, to maintain normal serum TSH concentrations."[19,p.4541] To make this recommendation, Kaplan et al. had to ignore the major finding of the four studies: that replacement therapies—in which clinicians adjust patients' dosages to maintain reference range TSH levels—are ineffective for many hypothyroid patients (and specifically for most patients in the four studies), leaving them to suffer from hypothyroid symptoms.

In their editorial, Kaplan et al. also appear to ignore a telling observation of their own: in one study, 15 thyroid cancer patients used TSH-suppressive dosages of thyroid hormone; their mood and cognitive function improved more than those of patients with autoimmune thyroiditis who used replacement dosages.[19,p.4540] This observation suggests that dosages higher than those dictated by the replacement concept more effectively relieve patients' hypothyroid symptoms. Other research has shown that patients report feeling better with TSH-suppressive dosages of thyroid hormone.[23][24][25] Moreover, psychiatrists report that dosages of T3 higher than replacement dosages augment the depression-relieving effects of antidepressants.[9][28][29][30][31][34] In addition, in a study of patients made hypothyroid by therapeutic destruction of the thyroid gland, some used TSH-suppressive dosages of thyroid hormone and others used T4-replacement. Those on TSH-suppressive dosages didn't gain excess weight; those on T4-replacement did. The researchers concluded that T4-replacement was the cause of the excess weight gain.[55] These published reports are consistent with thousands of cases in which hypothyroid patients recovered from their symptoms and other health problems with TSH-suppressive dosages of thyroid hormone *after* T4-replacement failed to help them.

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Clarifications:
Thyroid Hormone Replacement Therapies: Ineffective and Harmful for Many Hypothyroid Patients

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Complete Critique Published in *Thyroid Science* in 2006
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Supporting Documentation: Four 2003 Studies
of Thyroid Hormone Replacement Therapies:
Logical Analysis and Ethical Implications
by Dr. John C. Lowe

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Addenda to:
Four 2003 Studies of Thyroid Hormone Replacement Therapies: Logical Analysis and Ethical Implications

by Dr. John C. Lowe
Diplomate: American Academy of Pain Management
Director of Research: Fibromyalgia Research Foundation
drlowe@drlowe.com, drlowe@FibromyalgiaResearch.org

Addendum 1
Inaccurate Statements of the Endocrinology Researchers

In some statements, the researchers accurately reported what they found in their studies. In other statements, however, they quite inaccurately reported what they found. I've illustrated this below with specific excerpts.

In their abstract, Walsh et al. accurately wrote: "We conclude that *in the doses used in this study*, combined T4/T3 treatment does not improve well-being, cognitive function, or quality of life compared to T4 alone."[1,p.4543] (Italics mine, showing proper qualification.) At the end of their published paper, they accurately wrote, "In conclusion, we found no evidence that combined T4/T3-replacement *(in the dosage regimen used in this study*) resulted in improved well-being, cognitive function, quality of life, or increased thyroid hormone action on peripheral tissues compared with T4 alone."[1,p.4549] (Italics mine, showing proper qualification.)

However, they titled their published report with an invalid conclusion: "*Combined thyroxine/liothyronine [T4/T3] treatment does not improve well-being*, quality of life, or cognitive function *compared to thyroxine alone* . . . ."[1,p.4543] (Italics mine, showing lack of proper qualification.) The title of their article will function as an advertising banner providing a memorable and quotable sound bite implying that *no* approach to T4/T3 therapy works better than T4 alone.

Sawka et al. accurately wrote at the end of their published paper: "In conclusion, our data do not support the routine use of T3 in addition to T4 *to maintain euthyroidism* in hypothyroid patients who are receiving stable doses of levothyroxine hormone [T4], but who complain of depressive symptoms." (Of course, "to maintain euthyroidism" means to keep the TSH, free T4, and free T3 levels within their reference ranges, the very definition of "replacement" therapies.) And they accurately wrote, ". . . there is insufficient evidence to support changing the current approach of routinely using T4 alone *to maintain euthyroidism* in hypothyroid individuals."[2,p.4555] (Italics mine, showing proper qualification.)

These accurate statements of Sawka et al., however, are buried within the text of their published paper. Precious few doctors, patients, or science reporters will ever read them. At the end of their abstract, however—which many doctors, patients, and reporters will read—Sawka et al. quite inaccurately wrote: "In conclusion, the current data do not support the routine use of combined T4 and T3 therapy in hypothyroid patients with depressive symptoms."[2,p.4551]

Cassio et al. gave their readers a better chance—albeit little better—for an accurate understanding of their study finding. In their abstract, they wrote, "The combined treatment with T4 plus T3 seems not to show significant advantages, *at least in our experimental conditions*, compared with the traditional treatment with T4 alone in early treated [congenitally hypothyroid] infants."[4,p.1055] (Italics mine, to show their vague qualification. One would have to carefully read the rest of the authors' abstract or parts of their full report to understand that "*in our experimental conditions*" refers to their testing of only replacement therapies.) In the conclusion section of their full report, the authors make the same error as all the other researchers: "These preliminary data," they wrote, "seem to indicate that the combined treatment with T4 plus T3 does not show any significant advantage, at least in the short-term, compared with traditional treatment with T4 alone in early treated [congenitally hypothyroid] infants."[4,p.1059]

Clyde et al. failed to accurately state anywhere in their abstract the result of their study. They worded their conclusion so that readers are almost guaranteed to mistake their study of replacement therapies as an all-inclusive study of T4/T3 therapies compared to T4 alone. To wit, "Compared with levothyroxine [T4] alone, treatment of primary hypothyroidism with combination levothyroxine [T4] plus liothyronine [T3] demonstrated no beneficial changes in body weight, serum lipid levels, hypothyroid symptoms as measured by a [sic] HRQL questionnaire, and [sic] standard measures of cognitive performance."[3]

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Addendum 2

Endocrinologists’ Advice to Continue T4-replacement

Based on the studies showing that replacement therapies—including T4-replacement—are ineffective for many patients, the endocrinology researchers and other endocrinologists have recommended that T4-replacement remain the treatment of choice for most (Kaplan et al.[19,p.4541]) or all (Walsh et al.,[1,p.4549] Sawka et al.,[2,p.4555] and Clyde et al.[3]) hypothyroid patients. Below are the specific quotes.

Walsh et al. wrote, "Unless beneficial effects of combined T4/T3 treatment over T4 alone can be convincingly demonstrated by others, T4 should remain the standard treatment for hypothyroidism."[1,p.4549]

Sawka et al. wrote, ". . . there is insufficient evidence to support changing the current approach of routinely using T4 alone to maintain euthyroidism in hypothyroid individuals."[2,p.4555]

Kaplan et al. wrote in their editorial concerning the Walsh and Sawka studies, ". . . evidence is fading that adding T3 to T4 is beneficial in the long-term treatment of hypothyroid patients with autoimmune thyroiditis . . . . We do not believe that the current evidence supports the use of T3 for these patients, who are probably the largest group of hypothyroid patients."[19,p.4541]

Clyde et al. wrote, "This study supports these guidelines [of the American Association of Clinical Endocrinologists and the National Academy of Clinical Biochemists] by providing sound evidence that levothyroxine [T4] alone continues to be the most appropriate therapy for patients with primary hypothyroidism."[3]

These endocrinologists, then, recommend that T4-replacement should remain the treatment of choice for hypothyroid patients. The four studies at issue, however, are an admission that T4-replacement is ineffective for many hypothyroid patients. None of the endocrinologists’ recommendations based on the studies, however, contain any allowance for the needs of these patients for symptom relief and preemption of potentially lethal pathology. This obvious disregard for these patients’ needs raises serious ethical and humanitarian concerns.

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Addendum 3

Persistent Symptoms Among Patients Using Replacement Therapies

In the Clyde study, hypothyroid symptoms and/or their severity decreased about equally in patients treated with T4-replacement and those treated with T4/T3-replacement.[3] The improvement is inexplicable. It’s *highly* unlikely that the improvement was caused by T4-replacement. This is indicated by the fact that the patients, throughout the study, simply continued taking the dosage they’d been taking for at least six months before the study began. Cooper attributes the improvement to a placebo effect.[20] The replacement therapies, then, weren’t effective for the patients. Were it not for a placebo effect, natural variations in symptom intensity, or some unknown factor, the patients’ symptoms wouldn’t have improved at all.

The outcome of the other three studies shows that replacement therapies weren’t effective for most or all patients studied. In the Cassio study, for example, the researchers treated infants who had congenital hypothyroidism with either T4- or T4/T3-replacement. Testing showed that regardless of the type of replacement used, hypothyroid infants had lower neuropsychological scores than did control infants who weren’t hypothyroid.[4] Replacement therapies, then, through their ineffectiveness, retarded the neuropsychological development in these infants.

To take part in the Sawka study, patients had to have test evidence of depression. The researchers showed through their study that replacement therapies weren’t effective for these patients and left them depressed.[2]

In the Walsh study, typical symptoms suffered by patients—despite their use of T4-replacement for at least six months—were "tiredness, impaired well-being, or weight gain." Patients’ test scores were "worse" for somatic symptoms, anxiety, and insomnia.[1] The study showed that replacement therapies were ineffective for these patients and left them suffering from their symptoms.

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Addendum 4

Endocrinologists’ Warnings of Harm From TSH-Suppressive Dosages of Thyroid Hormone

Endocrinologists warn of three potential adverse effects from dosages of thyroid hormone greater than replacement dosages: decreased bone density, acute adrenal crisis, and atrial fibrillation.

Decreased Bone Density. Some eight years ago, I was surprised when bone density radiologists told me that a prevailing belief of endocrinologists was wrong: that TSH-suppressive dosages of thyroid hormone significantly reduce bone density. The available research literature confirmed that the radiologists were right. As they said, the evidence is that for most people, TSH-suppressive dosages of thyroid hormone *don’t* significantly reduce bone density or increase the risk for fractures. They were emphatic that there was *no evidence* that such dosages cause osteoporosis.

Considerable evidence, however, shows that decreased bone density is not a likely adverse effect from TSH-suppressive dosages of thyroid hormone. Psychiatric researchers reported that "supraphysiologic" (TSH-suppressive) dosages of T4 for one year and longer didn’t significantly reduce bone mineral density in pre- or post-menopausal women with mood disorders.[32][33] Similarly, reviews of studies of thyroid cancer patients taking TSH-suppressive dosages of thyroid hormone show that the patients don’t have reduced bone mineral density; the studies included men and pre- and post-menopausal women.[17] But still, despite overwhelming evidence to the contrary, some endocrinologists today continue to issue their warning.[27][36]

Acute Adrenal Crisis. Some endocrinologists also still warn that TSH-suppressive dosages of thyroid hormone may cause acute adrenal or Addisonian crisis, leaving a patient in shock and possibly dead. These warnings are based on a few published case reports.[80][81][82,p.872][83,p.813][85][86][87][88][89][90] For the most part, the cases involved patients in extraordinary circumstances. To extrapolate from these few reported cases to hypothyroid patients in general cannot be justified logically or scientifically.

My colleagues and I have observed hundreds of hypothyroid patients whose impaired adrenocortical function was unveiled by thyroid hormone therapy, resulting in acute cortisol deficiencies. The worst symptoms most patients experienced were weakness and fatigue. *We've not seen a single case of acute adrenal crisis.* To protect patients from potential harm, of course, we should always err on the side of safety, especially with patients who have Graves' disease.[82,p.872][83,p.813] But we err on the side of potential harm by keeping a patient's dosage of thyroid hormone too low from fear of this extremely rare adverse effect. (See section above titled "Presumptions of the Endocrinology Specialty: Instability of Desiccated Thyroid, Dangers of T3, and the Safety and Effectiveness of T4-replacement.")

Atrial Fibrillation. Today, the most often repeated warning against TSH-suppressive dosages of thyroid hormone involves the cardiac rhythmic disorder called atrial fibrillation. Researchers have conducted several studies and found that patients with the lowest TSH levels had an increased incidence of atrial fibrillation. The warning from the endocrinology specialty that has followed reports of this finding is that no patient taking thyroid hormone should have a suppressed TSH level. This warning, however, is based on an unjustified extrapolation from several studies. As Dr. Gina Honeyman-Lowe and I wrote in our 2003 book, *Your Guide to Metabolic Health*:

> Recently, endocrinologists have warned that TSH-suppressive doses of thyroid hormone increase the risk of atrial fibrillation three-fold. A number of studies showed that a certain set of people who had low TSH levels had a higher incidence of atrial fibrillation.
>
> But don't conclude from this finding that if you take a dose of thyroid hormone that suppresses your TSH level, you'll have atrial fibrillation. What endocrinologists—the main doctors who warn of this risk—don't bother to tell you is that these studies were done on elderly, sedentary individuals. In fact, in some of the studies, the patients were bedridden in nursing homes. In none of the studies did the researchers control for a heart-protective diet, nutritional supplements, or cardiovascular exercise to tolerance. The patients appear to have been in such poor health that they may have developed atrial fibrillation if they drank too much coffee each day. It's ludicrous and outrageously wrong to conclude that the results of these studies apply to healthier people using TSH-suppressive doses of thyroid hormone.[48,p.164]

Other endocrinologists and medical writers have reported less than a three-fold increased risk of atrial fibrillation, but they also violate the rule of accurate scientific reporting by extrapolating from the specific study population to a population with distinct relevant differences. In a 2004 issue of the *Annals of Internal Medicine*, for example, Helfand wrote: "About one fourth of patients receiving L-thyroxine for primary hypothyroidism are maintained unintentionally on doses sufficient to cause an undetectable TSH level.[22][64] Data from the Framingham cohort suggest that 1 excess case of atrial fibrillation might occur for every 114 patients treated with doses of L-thyroxine sufficient to suppress TSH.[64]"[65]

The implication of Helfand's two sentences is that a suppressed TSH level from excess thyroid hormone predisposes patients to atrial fibrillation. However, some of the patients in the Framingham study may have had low TSH levels because of pituitary hypothyroidism. Among those patients, atrial fibrillation may have resulted from too little thyroid hormone rather than too much. Because of this, we can consider his calculation an unjustifiable inference from the Framingham study. In addition, Helfand failed to note that the people in the Framingham study were, as the authors of the study specified, "elderly," and they weren't classified according to cardioprotective practices. His calculation, then, is illogical in that, as it's written, it extrapolates from one class of people prone to cardiovascular disorders to all patients who have low TSH levels. Helfand's statement constitutes inaccurate science reporting, and it is a disservice to the cause of scientific truth and quality patient care. (See section below titled, "Previous Atrial Fibrillation Studies: Possible Irrelevance to Hypothyroid Patients Taking TSH-Suppressive Dosages of Thyroid Hormone.")

Patients With Heart-Protective Factors Not Studied. The endocrinologists' warning of atrial fibrillation is unbalanced in terms of scientific evidence. In warning of atrial fibrillation, the specialists refer to no studies in which researchers controlled for factors known to increase resistance to atrial fibrillation. For example, in no studies have researchers controlled for heart-protective factors such as a non-atherogenic diet, cardiovascular exercise, or cardioprotective nutritional supplements.

Studies must be conducted to assess any adverse cardiac effects of TSH-suppressive dosages of thyroid hormone in patients whose hearts are protected by these factors. On principle, whether individuals do or don't avail themselves of these factors determines to a great degree their susceptibility to cardiac abnormalities such as atrial fibrillation. With a high degree of probability, the outcome of such studies will provide a more balanced view. Some hypothyroid patients with suppressed TSH levels are, of course, susceptible to atrial fibrillation. But cardioprotective factors render most patients more resistant to cardiac abnormalities. The incidence of atrial fibrillation with TSH-suppressive dosages of thyroid hormone will be strikingly lower than in people in general, and especially lower than in the sedentary elderly patients included in the previous studies.

What's needed is a study of a large population of people—both those protected by these factors and those not protected by them. If we include enough individuals, we're likely to find a bell curve distribution of cardiac responsiveness to TSH-suppressive thyroid hormone dosages.

On the right flange of the bell will be a diminishing percentage of people whose hearts are progressively more responsive to a particular TSH-suppressive dosage of thyroid hormone. Correspondingly, that diminishing percentage of people in the right flange will have a progressively higher susceptibility to cardiac abnormalities in response to that dosage.

On the left flange of the bell would be a diminishing percentage of people whose hearts are progressively less responsive to the particular TSH-suppressive dosage. Correspondingly, that diminishing percentage of people in the left flange would exhibit a progressively lower incidence of cardiac abnormalities in response to the dosage.

In other words, people on the right side of the curve would be progressively more susceptible to cardiac abnormalities, and those on the left would be progressively more resistant to abnormalities. The current method for establishing the reference range for the TSH and thyroid hormone levels ignores this mathematical and practical phenomenon dictated by the central limit theorem, which has accurately predicted anything and everything human beings have measured enough times in the past 270 years. To continue to ignore it—as do those who establish the reference ranges—is to doom practicing physicians to an unnecessarily high failure rate in the diagnosis and treatment of hypothyroid patients.

From consideration of the central limit theorem, some diminishing percentage of hypothyroid patients clearly have some relative degree of tissue resistance to a particular dosage of thyroid hormone that most other patients are more responsive to. Normal metabolism in these patients is possible *only* with dosages of thyroid hormone that are overstimulating to most other patients. To deny them those dosages is to consign them to lifelong hypometabolism with all its attendant adverse health effects. This is truly inhumane. They are thusly consigned, however, when restricted to replacement dosages (which for them are clearly inadequate) to protect them from the atrial fibrillation that only patients on the right flange of the bell curve would experience.

Previous Atrial Fibrillation Studies: Possible Irrelevance to Hypothyroid Patients Taking TSH-Suppressive Dosages of Thyroid Hormone. Aside from the bell curve phenomenon, a methodological issue may render the studies of atrial fibrillation irrelevant to patients taking TSH-suppressive dosages of thyroid hormone as a medication. The studies involved patients whose TSH levels were suppressed without the use of thyroid hormone. These patients, as a group, may differ in some relevant way from patients taking thyroid hormone from an external (exogenous) source. If they do differ in a relevant way, they may *not* share an increased risk of atrial fibrillation with patients who have endogenously suppressed TSH levels.

I anticipate the criticism that this distinction isn't important. My retort is that such distinctions are often made in defense of T4-replacement therapy. Recently, for example, Kaplan et al. noted that from using higher-end thyroid hormone dosages, thyroid cancer patients' mood and cognitive dysfunction improved more than that of autoimmune thyroiditis patients.[19,p.4540] The cancer patients were taking higher dosages of thyroid hormone than the thyroiditis patients; in fact, about half of the cancer patients were using dosages that suppressed their TSH levels. As in other studies,[23][24][25][28][29][30][31][34] the thyroid cancer patients undoubtedly improved more because of their higher thyroid hormone dosages. Kaplan et al. conjectured, however, that thyroid cancer patients improved more—not because of their higher dosages of thyroid hormone—but because they differed in some relevant but undetermined way from autoimmune thyroiditis patients.[19,p.4540] Methodological issues remain relevant no matter who draws attention to them.

Conclusion Regarding Warnings. Available scientific evidence shows that the endocrinology specialty's sweeping warnings against TSH-suppressive dosages are unwarranted. Scrutiny of the evidence shows that the specialty has exaggerated the warnings in the extreme, and it has generalized them into invalid universal propositions. The specialty's failure to show equal concern about the adverse effects of patients taking too little thyroid hormone suggests that its major concern is not protection of patients, but instead, perpetuation of the widespread practice of T4-replacement.

Patient Safety Must Be Based on Evaluation of the Individual's Tissue Responses to Thyroid Hormone. I want to emphasize that *the responsiveness of different patients' tissues to a particular dosage of thyroid hormone varies widely*.[18,p.16] A particular dosage for some patients is overstimulating, while for others, it regulates metabolism perfectly—yet for still others, it is understimulating. In short, for any particular dosage of thyroid hormone, we'll find a predictable bell curve of tissue responsiveness in the population, if we test enough subjects.

In view of this, the only rational approach to safe and effective thyroid hormone therapy is a highly individualized one, based on how each patient's tissues respond to a particular dosage. This cannot be accomplished by deductions based on levels of TSH or thyroid hormone, as the endocrinology specialty implies. The TSH level does change in response to changes in thyroid hormone dosage, but not within a range considered clinically relevant. In contrast, the resting metabolic rate, calculated from patients' resting VO2 consumption, is a measure of tissue responsiveness that is *highly* sensitive to slight changes in thyroid hormone dosage.[79] Therefore, compared to the resting metabolic rate and other measures of tissue response, TSH levels are inferior as a method of fine-tuning thyroid hormone dosages.

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Addendum 5

About Dr. Hutton

Dr. James H. Hutton was the author of the 1966 book titled *Practical Endocrinology*. At that time, he was consulting endocrinologist at the Illinois Central Hospital. He had been professor of endocrinology at the Chicago Medical School, and past president of the Chicago Medical Society.

Two physicians wrote introductory comments about Dr. Hutton in *Practical Endocrinology*. Dr. Ernest Olson wrote, "The author has been a consultant in endocrinology to the Illinois Central Hospital since 1920. It has been my privilege to observe the development of this specialty in our hospital since 1923 under his direction."[18,p.v]

Dr. Chester Guy wrote, "The author's long and rich experience in this field [endocrinology], together with his ability as a teacher, prompted the request that he prepare a series of lectures for the house staff of the hospital. These proved so interesting and practical that he was urged to incorporate them in book form under this appropriate title. It is believed that this volume, with its historical and humorous observations, and *its directions for proven therapies*, will merit a place in the libraries of those whose practices involve problems of the endocrine glands."[18,p.v] (Italics mine.)

Selected Letters in Response to

Thyroid Hormone Replacement Therapies: Ineffective and Harmful for Many Hypothyroid Patients

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[Responses are posted in reverse chronological order. The latest responses come first. Earlier ones are further down the page.]

On June 19, 2004, Dr. John Dommisse sent an email to Dr. Lowe in response to his critique of the replacement studies. Dr. Dommisse is a physician who practices nutritional, metabolic, and psychiatric medicine, and who hosts a popular telemedicine website. He is a member of the Endocrine Society, which publishes the *Journal of Clinical Endocrinology and Metabolism* (*JCEM*). *JCEM* published two of the replacement studies in 2003, and an editorial in which the authors reiterated the invalid conclusion of the endocrinologists who conducted the studies.

Dr. Dommisse's email included a copy of a letter he'd written to the Editor of *JCEM*. He wrote the letter in response to the reports of the replacement studies. *JCEM* declined to publish his letter, so he gave Dr. Lowe permission to publish it here as support for Dr. Lowe's critique.

In his email to Dr. Lowe, Dr. Dommisse wrote, "*JCEM* would not even publish a (longish, admittedly) LETTER that I wrote to the editor in response to that spate of bogus articles!"[1]

Dr. Lowe replied:

> I am not surprised that *JCEM* didn't publish your letter. I'm not surprised despite your letter's precise relevancy to the articles about the replacement studies, despite the excellent points you raised about treatment and avoiding adverse effects, and despite your clear prose. We became convinced long ago that, regarding the diagnosis and treatment of hypothyroidism, most major medical journals are not published in the pursuit of truth. If they were, they would provide for debate of dissenting views—as is traditional in real sciences. Instead, in our view, the purpose of the journals, in regard to the diagnosis and treatment of hypothyroidism, is to perpetuate medical acceptance of financially profitable beliefs and to censor dissenting views that might threaten financial markets nourished by those beliefs. What bothers me most is

> that, in my opinion, to serve those two purposes, those who decide what will and won't be published in those journals must carry on with cavalier disregard for the pernicious impact of those beliefs on humanity.[2]

Dr. Dommisse's full letter to the Editor of the *Journal of Clinical Endocrinology and Metabolism*

Dr. John Dommisse's Website

References

1. Dommisse, J.: Personal written communication with Dr. John C. Lowe. June 19, 2004.
2. Lowe, J.C.: Personal written communication with Dr. John Dommisse. June 19, 2004.

Subj: Brief Comment on Critique of Thyroid Hormone Replacement Studies
Date: 6/8/2004 4:47 PM Mountain Daylight Time
From: piek@waitrose.com
To: DrJohnLowe@aol.com
Sent from the Internet

The original Bunevicius research found benefits for T3/T4 over T4 and was followed up by a further analysis (*Int. J. Neuropsycopharmacology,* 2000, 3:167-174) which demonstrated that these benefits applied only to those on TSH-suppressive doses of thyroid hormones, particularly for thyroid cancer. Each of the four replacement studies tested patients on lower doses.

However,

"Combined Thyroxine/Liothyronine [T4/T3] Treatment Does Not Improve Well-Being, Quality of Life, or Cognitive Function Compared to Thyroxine Alone: A Randomized Controlled Trial in Patients with Primary Hypothyroidism" (Walsh et al. *JCEM* 88(10):4543-4550)

is a classic. ". . . subjects attended after an overnight fast and before taking T4 or study medication (i.e. 24 h after the previous dose)." Their data shows that the T3/T4 group had lower T3 levels than the T4 group and in the Discussion section they acknowledge the 24-hour half life of T3! Duh!!!

Jim Harwood. piek@waitrose.com

In response to Dr. Lowe's critique of replacement studies, a patient wrote to Dr. Gina Honeyman-Lowe on June 8, 2004. The patient described her remarkable improvement after switching from T4-replacement to T3. She expressed understandable outrage at the closed minds within the medical community. She had remained ill for years on Synthroid.

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Continuation: Four 2003 Studies of
Thyroid Hormone Replacement Therapies:
Logical Analysis and Ethical Implications
by Dr. John C. Lowe

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Potential Harm From TSH-Suppressive Dosages of Thyroid Hormone

In arguing that physicians should permit some hypothyroid patients to use TSH-suppressive dosages of thyroid hormone, it is incumbent upon me to justify the argument. To do so, I must explain two contradictory propositions.

> The first, espoused by the endocrinology specialty, is that:
> only thyroid hormone replacement is safe for hypothyroid patients.
> And the second, my proposition, says that:
> for a subset of hypothyroid patients, TSH-suppressive dosages of thyroid hormone are safe and necessary for health.

The available evidence shows the first proposition to be false and the second true. I'll show this first by

> (1) referring readers to the section below titled "Presumptions of the Endocrinology Specialty: Instability of Desiccated Thyroid, Dangers of T3, and the Safety and Effectiveness of T4-replacement,"
>
> (2) presenting evidence that a subset of patients uses TSH-suppressive dosages with impunity, and
>
> (3) providing a plausible theoretical explanation for their safe and effective use of suppressive dosages.

A fitting introduction to the evidence for my viewpoint on TSH-suppressive thyroid hormone therapies is a 38-year-old statement by endocrinologist James H. Hutton. (For comments on Dr. Hutton, see Addendum 5) His statement is on alleged harm from the use of thyroid hormone.

> Thyroid is a much maligned agent. Certainly it should be administered only under the supervision of a physician, but the danger likely to result from taking it has been portrayed in such lurid fashion that many medical men seem hesitant about giving it. As a matter of fact, overdosage seldom occurs. Signs of such an event are so easily recognized before any damage is done that any medical man should use it wherever he believes it is indicated.[18,p.16]

Dr. Hutton continued,

> The tachycardia, tremor, palpitation and increased nervousness [from overdosage] are easily recognized so that one may accurately administer it without resorting to frequent determination of the BMR, etc. *The tolerance for it varies over an extremely wide range with different patients.* [Italics mine.] Patients much in need of it may tolerate less than one grain [of desiccated thyroid] per day, others who seem to need it no worse, tolerate up to 60 grains per day without any discernible ill effects. This, of course, could have been due to a difference in absorption of the drug from the gut.[18,p.16]

Hutton wrote that 120-to-180 mg (approximately 2-to-3 grains) daily was optimal for almost all myxedematous patients.[18,p.76] I cite the 60 grains not as a recommendation for any patient, but as a segue to consideration of a concept currently lacking in decision-making about thyroid hormone dosages within conventional medicine practice. The concept is that of a normal error or variance (bell curve) distribution of tissue responsiveness to thyroid hormone among patients.

The scores of everything we can measure, when we measure enough instances, fall into a bell curve distribution. This is true of measurable phenomena classified in virtually any way, such as social (ethnic and racial prejudice), psychological (scores on an aptitude test), anatomical (heights of adult males and females), molecular (molecular weight of a chemical), environmental (yearly temperature variations), economic (stock market variations), and physical (mechanical force needed to bend apparently identical steel rods). And we can, on principle, expect that within the population of hypothyroid patients, tissue responsiveness to a particular dosage of thyroid hormone falls into a bell curve distribution. We can expect this even while allowing for variable responsiveness of different tissues within individual patients.

Central Limit Theorem and the Ineffectiveness and Dangers of Replacement Therapy for Many Patients

In laboratory medicine, current practice for the most part ignores the need of some patients for dosages of thyroid hormone that exceed other patients' needs. The standard of practice implies that the optimal dosage for all patients is the amount that keeps the TSH within its current reference range. But this implication conflicts with what we can reasonably predict from the central limit theorem of mathematics. The theorem says that for samples that are sufficiently large, the distribution of means is almost always more or less normal. The theorem, I believe, provides an explanation for the ineffectiveness and harm of thyroid hormone replacement for many patients, and for them, the effectiveness and safety of TSH-suppressive dosages.

I don't mean to imply that laboratory medicine specialists calculate reference ranges without considering the normal variance distributions; indeed, they base the ranges on the 95% confidence intervals of the distributions.[41] I explicitly contend, however, that clinicians, as standard practice, don't consider the normal distribution of variances in interpreting laboratory thyroid function test results or in making dosage decisions.

The central limit theorem predicts that repeated measurements (reported as the means of multiple samples) of any phenomenon produce readings that vary around a mean, so that they form a normal distribution. Applied to the concept of variable tissue responsiveness, the theorem predicts the following proposition: On the left slope and flange of the bell curve of tissue responsiveness, a progressively decreasing percentage of hypothyroid patients require progressively larger dosages of thyroid hormone to prevent symptoms of hypothyroidism, and ward off pathologies secondary to hypothyroidism. The theorem also predicts that the tissues of this progressively decreasing percentage of patients are progressively more resistant to overstimulation by progressively larger dosages of thyroid hormone.

Thus, the theorem predicts that what to some patients (on the right slope and flange) is an overstimulating dosage of thyroid hormone is to others (on the left slope and flange) innocuous. Our clinical experience and studies of potential adverse effects of TSH suppression bear this out. So do studies in which only a small percentage of patients had adverse effects to TSH-suppressive dosages of thyroid hormone, while most patients had no such effects. Those who had adverse effects represent the right outer slope and flange of the bell curve, where patients' tissues are more responsive to a particular dosage of thyroid hormone than are most other patients' tissues.

Unfortunately, many researchers mistakenly conclude that since a *subset* of patients has adverse effects from TSH-suppressive dosages of thyroid hormone, physicians should protect *all* patients by denying them such dosages. What these researchers apparently fail to comprehend is a point of crucial importance to the health and safety of the subset of patients on the left end of the curve: for these patients, TSH-suppressive dosages are both harmless and necessary to their health and well-being. Of course, in the vein of patient safety, we must be ever vigilant in clinical practice for potential adverse effects, even in this left-end subset of patients. But it is equally important in the vein of safety that we be cognizant that their health and well-being are assured *only* when they use the TSH-suppressive dosages that are harmful to patients on the right end of the curve.

The endocrinology specialty overall ignores the predictable phenomenon of a normal distribution of tissue responsiveness among the population of hypothyroid patients. Consistent with ignoring the phenomenon, the specialty implies or explicitly states that unless a patient has thyroid cancer, he/she shouldn't use a TSH-suppressive dosage of thyroid hormone. The reason the specialty gives is that the dosage is highly likely to harm the patient. For thyroid cancer patients, the specialty argues, the benefits of TSH-suppressive dosages are worth the risks, although they are still not preferable.

Consider, however, a report by nuclear medicine specialists of a man with well-differentiated thyroid cancer.[15] For ten years, he had taken a high dosage of T4 to suppress his TSH level. During that time, his dosage ranged between 0.9-to-3.3 mg (900-to-3300 mcg T4; roughly equivalent to 44.6 grains of desiccated thyroid, which is close to the 60 grains that some patients tolerate well, according to Hutton). The authors wrote, "*He was essentially asymptomatic and suffered no apparent ill effects* from this prolonged and markedly excessive dosage of L-thyroxine. The literature lists a wide range of ill effects from both chronic and acute thyroid hormone overdosage *but also records many examples of tolerance to excessive levels of exogenous thyroid hormone*." (Italics mine.)

Treatment of thyroid cancer patients with TSH-suppressive dosages of thyroid hormone has provided a population of patients that enables us to examine the likelihood of harm from such dosages. The general belief within the endocrinology specialty is that for thyroid cancer patients, suppressing the TSH to an undetectable level is acceptable, as long as patients avoid "clinical thyrotoxicosis."[16,p.1150] Researchers have now conducted many studies of these patients to learn whether the TSH-suppressive dosages adversely affect their bones and hearts.

The research literature contains many studies of potential adverse effects of TSH-suppressive dosages on bone. What we've learned from these studies provides us with what could evolve into principles for the safe use of such dosages by a subset of hypothyroid patients—those for whom replacement dosages aren't effective, and therefore not safe (see section below titled "Presumptions of the Endocrinology Specialty: Instability of Desiccated Thyroid, Dangers of T3, and the Safety and Effectiveness of T4-replacement").

Table 1. Risk factors for decreased bone mineral density*

Low calcium
Low vitamin D intake or low exposure to sunlight

That a patient uses a TSH-suppressive dosage of thyroid hormone *doesn't* mean that the patient will definitely have reduced bone mineral density. Whether he or she does or doesn’t depends largely on another variable: the number of other risk factors for reduced bone density that impinge on the patient. Susceptibility in an individual patient, then, is the algebraic summation of the presence or absence of multiple risk factors. I’ve listed the most common ones[39][40] in Table 1. It’s worth noting here that the variance within any normal distribution is caused by the influences of many small random effects on the measured variable. Risk factors for reduced bone density are such random effects.

Estrogen deficiency
Small body stature
Low body weight
Advanced age
Tobacco smoking
High alcohol consumption
Use of pharmacologic dosage of corticosteroids
Too little back-stretching
Too little high-impact and/or weight-bearing exercise

*No authors listed: Osteoporosis-prevention, diagnosis and treatment: a systematic literature review: SBU conclusions and summary. *Lakartidningen*, 100(45):3590-3595, 2003.[39]

Yoshimura, N.: Exercise and physical activities for the prevention of osteoporotic fractures: a review of the evidence. *Nippon Eiseigaku Zasshi*, 58(3):328-337, 2003.[40]

To put the role of risk factors into proper perspective, consider a bell curve of bone responsiveness to TSH-suppressive dosages of thyroid hormone. On the right end of the curve, an increasing number of risk factors for reduced density renders a decreasing percentage of patients progressively more susceptible to reduced bone mineral density from TSH-suppressive dosages of thyroid hormone. On the left end of the curve, a decreasing number or absence of risk factors for reduced bone density renders a progressively decreasing percentage of patients progressively more resistant to reduced bone mineral density from TSH-suppressive dosages.

Before treating a patient with a thyroid hormone dosage greater than a replacement dosage, we don't know where his or her tissues fall within the bell curve of tissue responsiveness to the hormone. As the four studies at issue here show, presuming that all hypothyroid patients' tissues fall close to the mean of tissue responsiveness to thyroid hormone causes some patients to continue to suffer from hypothyroid symptoms. For some—the diminishing percentage who fall on the right flange of the curve—a particular TSH-suppressive dosage will cause thyrotoxicosis; for others—the diminishing percentage on the left flange—that same dosage is necessary for normal metabolism and freedom from hypothyroid symptoms. The further out these patients' tissue responsiveness falls in the left-side flange of the bell curve, the more resistant to thyrotoxicity they are, and the less effective thyroid hormone replacement is for them.

The 95% confidence interval that lab pathologists use to establish reference ranges is a mathematical calculation that leaves 2.5% of patients on each end of the distribution. Standard practice in medicine is to conclude that lab values within the 95% interval are "normal," and that those in the 2.5% on each end of the distribution are "abnormal." This conclusion is an *arbitrary social convention*—one that ignores the progressive variance that occurs as lab values proceed outward bilaterally through two standard deviations from the mean. (In general, physicians arbitrarily consider lab values that fall within two standard deviations of the mean "normal.") Patients whose tissue responsiveness falls progressively further out on the left side of the distribution are progressively more susceptible to developing symptoms of hypothyroidism. This is true despite their tissue responsiveness being within two standard deviations of the mean. Much to the patients' misfortune, however, most physicians will conclude that their symptoms can't be caused by hypothyroidism because their TSH and thyroid hormone levels are within the "normal" reference ranges—that is, their respective 95% confidence intervals.

Appreciation of the bell curve distribution of tissue responsiveness to thyroid hormone compels us to acknowledge the existence of a diminishing percentage of patients on the left side of the curve whose tissues are progressively less responsive to a dosage of thyroid hormone that keeps most hypothyroid patients symptom-free. These patients require higher dosages of thyroid hormone—for many, TSH-suppressive dosages—to maintain normal metabolism and health.

Correspondingly, these patients' tissues will predictably be progressively more resistant to dosages of thyroid hormone that for most other patients are thyrotoxic.

In my view, the recent four replacement therapy studies addressed patients on the left-side flange of the bell curve. The studies showed that replacement dosages are insufficient for relieving their hypothyroid symptoms. The studies are *ipso facto* evidence for a humanitarian imperative: that researchers and physicians now accommodate these patients' need for dosages of thyroid hormone larger than those dictated by the concept of replacement therapies.

Presumptions of the Endocrinology Specialty: Instability of Desiccated Thyroid, Dangers of T3, and the Safety and Effectiveness of T4-replacement

The endocrinology specialty bases some of its most influential pronouncements on presumption—a basis that hardly justifies the certitude with which it expresses the pronouncements. Three presumptions appear to sustain the practice of T4-replacement. The presumptions are that desiccated thyroid is unstable, that T3 is troublesome and dangerous, and that T4-replacement is invariably safe and effective.

Instability of Desiccated Thyroid

Since the 1960s, the endocrinology specialty has advocated and even enforced only the use of T4-replacement in lieu of desiccated thyroid as a treatment for hypothyroidism. According to endocrinologists, the reason for this advocacy and enforcement is that the potency of desiccated thyroid is difficult to standardize. That is, the endocrinologists claim that too often, desiccated thyroid tablets don't contain the amount of thyroid hormone reported on the label. They argue that the potency of synthetic T4 is more stable.[42] That synthetic T4 products are more stable, however, is a mere presumption. I can find no studies in which the stability of desiccated thyroid and synthetic T4 were compared. When I searched for studies in *Medline*, using the keywords "desiccated thyroid," "Armour," "stability," and "potency," I found no studies. But when I searched for "Synthroid" and either "stability" or "potency," I found two abstracts.[67][68] In one, the authors state, "Levothyroxine tablets, 50 microg, have been marketed for many decades but have had numerous recalls due to degradation and failure to meet potency."[67]

The specialty has tenaciously endorsed a T4 product called Synthroid, perpetuating the belief that it is the pinnacle of potency-stable medications. Shomon[46] and I[47] have reported, however, that the FDA has repeatedly recalled batches of Synthroid because tablets from the batches were "subpotent." This term means that tablets didn't contain the amount of T4 claimed on the label. Despite this public record of serious problems with potency, representatives of the endocrinology specialty have doggedly continued their endorsement of Synthroid—and *only* Synthroid.

The fact is that all thyroid hormone products, both animal-derived and synthetic, are unstable compared to many other drugs. Thyroid hormones consist of iodine atoms bound to the amino acid tyrosine. The iodine atoms fairly easily separate from the tyrosine. Because of this, it's prudent for both doctors and patients to be vigilant for subpotent tablets or capsules. The reassurance of the endocrinology specialty that Synthroid is more stable than other products is groundless. Because it misleads doctors and patients, often to the patients' detriment, the specialty should cease to make this pronouncement.

Dangers of T3

The endocrinology specialty has long opposed the use of products that contain T3. The basis of its opposition, so it claims, is the resulting brief peak blood level of T3. Members of the specialty glibly state that the peak level is in the "thyrotoxic range"[84,p.1225] and that this peak level causes heart palpitations that trouble patients. They further state that the peak level may adversely affect the heart. But, these members resound, by using Synthroid patients can avoid these problems.

The specialty's claim that T3 causes these problems is a mere presumption; it is contradicted by the reports of researchers with extensive clinical experience with T3. Psychiatric researchers whose patients use T3 point out that it is generally well-tolerated.[35] The experience of my research group agrees with this observation. For some fifteen years, our treatment team has worked directly with hundreds of patients using combined T4/T3 products or T3 alone. Our observations during that time dispute the warning that palpitations are a problem for patients who use T3-containing products. Palpitations in these patients are *exceedingly* rare. When a patient has experienced palpitations, they have been minor and of little or no concern to the patient. The palpitations have also been of no clinical significance. It's noteworthy that the researchers of the four studies, as well as those of three other studies comparing the effectiveness of T4 and T4/T3-replacement, didn't report that their study patients were troubled by palpitations.[1][2][3][4][5][6][7]

I can find no study that members of the specialty have conducted confirming its prediction of adverse effects from T3. Only last year, endocrinologists Kaplan, Sarne, and Schneider wrote: ". . . the possible long-term risks of elevated or fluctuating T3 levels have not been evaluated."[19,p.4541]

Systematic studies have not conclusively ruled out long-term adverse effects. But many patients have used T3 for many years without apparent adverse effects. We have, then, a positive anecdotal record and no long-term safety studies showing that T3 is harmful. Regardless, the specialty has warned of potential harm in a manner that has generated irrational fear of T3 among physicians. It's common, for example, for patients who've asked their doctors to prescribe T3 to hear the reply, "If you take T3, you're going to have a heart attack and die!"[48,p.10]

It goes without saying, of course, that caution is necessary with patients who have fragile cardiac conditions. This is especially true when such a patient is using a product containing T3, since T3 directly affects the myocardium.[66] But *potential* harm from T3 is not *actual* harm, and the endocrinology specialty has so blurred the distinction that most other physicians—and perhaps they themselves—don't know the difference.

Safety and Effectiveness of T4-replacement Therapy

Just as the endocrinology specialty's objections to the use of desiccated thyroid and T3 are based on presumption, so is its long-standing dictum that T4-replacement is always safe and effective. Some members of the specialty have been steadfastly convinced of the fail-safe effectiveness of T4-replacement. When patients complain of continuing hypothyroid symptoms despite using "adequate T4-replacement," these members argue that something other than a thyroid hormone deficiency must be causing their symptoms.

Witness, for example, statements by thyroid surgeon Richard Guttler: "We have the most accurate thyroid testing, and if you test normal, and have symptoms, most likely your symptoms aren't due to abnormal thyroid balance." And further, "[I] rely on accurate thyroid blood testing. The thyroid tests are abnormal way before [patients] have 'thyroid related symptoms'. *Other similar symptoms, such as fatigue, and weight gain are not thyroid related if the testing is stable and normal.*"[49] (Italics mine, and incorrect punctuation is Guttler's.)

Similarly, consider a comment of influential endocrinologist M.I. Surks in a chapter on treating hypothyroidism in the widely used thyroidology textbook, *Werner's The Thyroid*: "Notwithstanding the physician's assurance that the T4 dose is optimal, and the demonstration that serum TSH has decreased into the normal range, these patients may ask for a larger dose or take a larger dose on their own initiative. In this setting, *the patient should be reassured that the T4 dose prescribed is appropriate, and other causes of the patient's complaints must be investigated.*"[43] (Italics mine.)

Surks' advice to reassure the patient that his or her dosage "is appropriate" *presumes* that the patient's T4 dose is adequate for his or her individual needs. His advice that "other causes of the patient's complaints" be investigated suggests a preconceived notion that replacement dosages of T4 are infallibly effective. In addition, his advice, like that of Guttler, implies that if a patient has hypothyroid-like symptoms despite using T4-replacement, the symptoms are probably caused by some other disorder.

Endocrinologists can maintain this belief only by ignoring published evidence showing it to be false.[8][68] Consider, for example, a finding of Fraser et al.[68] The study result reveals the harm many hypothyroid patients suffer when their physicians make dose decisions based on TSH levels.

The Fraser Study. Three physicians experienced in diagnosing and treating hypothyroidism assessed 148 hypothyroid patients on T4-replacement. The physicians used the Wayne clinical diagnostic index,[69] an objective tool for deciding whether a patient's thyroid hormone therapy is adequate, excessive, or insufficient. Statistical tests showed that the three physicians' judgment didn't differ in classifying patients.

Among the 148 patients, 108 were clinically normal. This means they were taking enough T4 to be free from symptoms of hypothyroidism. Despite this, 53 of them (49%) had TSH levels below the lower limit of the reference range. Conventional physicians, of course, would interpret their TSH test levels as evidence that the patients were "hyperthyroid" or "thyrotoxic." This mistake is understandable when prominent endocrinologists—Dr. Anthony Toft, for example—have incorrectly termed a low TSH as a "thyrotoxic" level.[70,p.91] And probably most physicians would have required these patients to lower their dosages of T4 to raise their TSH levels—even though the patients were clinically normal. As a result of lowering their dosages, however, some of them, and perhaps all, would have begun suffering from hypothyroid symptoms and risked developing diseases from too little thyroid hormone regulation.[37]

Among the 148 patients, 18 were clinically hypothyroid. This means they were taking too little T4 to keep them from suffering from symptoms and signs of thyroid hormone deficiency. Despite being clinically hypothyroid, 3 of the 18 patients (17%) had TSH levels below the lower limit of the reference range. Most physicians would have required these patients to lower their T4 doses to raise their TSH levels. Doing so would surely worsen their symptoms and signs of hypothyroidism,[68,p.809] and would make them more susceptible to potentially fatal diseases associated with hypothyroidism.[37]

The suffering of these patients and their potential for pathology would result from the obstinate demand by the endocrinology specialty that physicians titrate hypothyroid patients' T4 doses by their TSH levels—and *only* by those levels. Of course, some endocrinologists also advise other physicians to use the free T4 in making dosage decisions. The Fraser study showed that among the 18 clinically hypothyroid patients, the free T4, like the TSH, led to a false interpretation of the patients' status. In 4 of the 18 patients (22%), the free T4 was above the upper limit of the reference range. This gave a false signal that the patients were overtreated, when it fact they were undertreated.

Results of the Fraser study should alert all physicians to the potential for harming their patients through following the practice guidelines of the endocrinology specialty. Basing their dosage decisions on TSH and free T4 levels instead of clinical assessment will leave many patients undertreated—a condition that is hazardous to the patients' health (see following section).

Consequences of the Presumption That T4-replacement Is Invariably Safe and Effective

As I wrote above, the endocrinology specialty maintains that if patients with hypothyroid-like symptoms have "normal" TSH levels, their symptoms must be caused by something other than a thyroid hormone deficiency. It is precisely this false belief that has led to the "new diseases" of the past 30 years. Prominent among these are so-called "fibromyalgia" and "chronic fatigue syndrome." Considerable evidence indicates that inadequate thyroid hormone regulation is the major underlying causative factor in these supposed new disorders. For example, the only studies in which patients with these diagnoses have fully and lastingly recovered are those in which they underwent thyroid hormone therapy.[10][11][12][13][14][45][71][72][73]

As Dr. Gina Honeyman-Lowe and I have argued with substantial documentary evidence,[44][50][51] the disorder underlying most patients' fibromyalgia is inadequate thyroid hormone tissue regulation. Our data indicate that the fibromyalgia symptoms and signs of approximately 90% of patients are features of hypothyroidism and/or thyroid hormone resistance. In most cases, patients' thyroid disease is complicated by low physical fitness levels, nutritional deficiencies, the dysglycemic and proinflammatory effects of poor diet, and the adverse metabolic effects of various medications other than thyroid hormone prescribed to control symptoms of hypothyroidism and/or thyroid hormone resistance. The number of patients with chronic, widespread pain (a classic symptom of hypothyroidism) increased in the mid-1970s to a point that rheumatologists began to take notice. This occurred shortly after endocrinologists, in 1973 and 1974, recommended cutting hypothyroid patients' thyroid hormone dosages in half. This reduced patients' dosages from the equivalent of 200-to-400 mcg of T4 to 100-to-200 mcg.[74][75] The purpose was to raise the patients' TSH levels. (The new TSH test had recently come into widespread use.) The rheumatologists unquestioningly accepted the endocrinologists' pronouncement that the patients' reference range TSH levels ruled out thyroid hormone deficiency as the cause of their chronic, widespread pain. Eventually, the rheumatologists gave this classic hypothyroid symptom the name "fibromyalgia."[76]

The numbers of patients with overwhelming chronic fatigue steeply increased in the late 1970s. Eventually, researchers named this classic hypothyroid symptom "chronic fatigue syndrome." As standard practice at this time, physicians had come to adjust patients' thyroid hormone dosages to keep their TSH levels within the reference range.[77] As Dr. David Derry wrote in the *British Medical Journal*, "In 1973 thyroidologists officially endorsed the newly designed TSH test for thyroid function . . . . The TSH test caused the appearance six years later of chronic fatigue and fibromyalgia."[78]

The endocrinology specialty has been completely deaf to our reports that inadequate thyroid hormone regulation is the major cause of symptoms diagnosed as fibromyalgia and chronic fatigue syndrome.[44] The reason for the deafness is the belief expressed in the quotes above by Guttler and Surks—that symptoms of patients who have "normal" TSH levels can't possibly be due to too little thyroid hormone regulation. Our reports that this is false, and that the symptoms of fibromyalgia and chronic fatigue syndrome are those of inadequate thyroid hormone regulation, are supported by a growing body of evidence.

Continued Suffering of Many Patients on T4-replacement

Three survey studies have shown that many patients on "adequate T4-replacement" continue to suffer from symptoms and signs of hypothyroidism. As one would expect, these patients were dissatisfied with their thyroid hormone therapy.[52][53,p.153][54]

In a study of 37 patients with subclinical hypothyroidism, T4-replacement improved patients' memories. But the patients had no measurable improvement in other symptoms or their health-related quality of life.[38]

Results of the survey studies and the study of subclinical hypothyroid patients are backed up by three of the four studies at issue.[1][2][3] Patients who still had hypothyroid symptoms despite being treated with T4-replacement were included in the studies. Neither T4- nor T4/T3-replacement relieved their symptoms. In another of the studies, researchers compared the psychomotor development of infants who had congenital hypothyroidism to that of infants who had normal thyroid function. The hypothyroid infants had impaired psychomotor development. Neither T4- nor T4/T3-replacement relieved the infants' impairment.[4]

Psychiatric researchers reported that patients taking antidepressants often remain depressed when they are on T4-replacement—even TSH-suppressive dosages. Adding T3, further depressing the TSH level, then relieves the patients' depression.[30]

Researchers recently reported measuring changes in weight of two groups of patients after they had therapeutic destruction of their thyroid glands. The first group, thyroid cancer patients, used TSH-suppressive dosages of thyroid hormone after the destructive therapy. They didn't gain weight. The second group, Graves' disease patients, used T4-replacement after destructive therapy. They did gain excessive weight. The researchers concluded, "The excessive weight gain in patients becoming hypothyroid after destructive therapy for Graves' disease suggests that restoration of serum TSH to the reference range by T4 alone may constitute inadequate hormone replacement."[55]

Increased Incidence of Disease and Medication Use Among Patients on T4-replacement

Researchers recently conducted the first large, community-based study in the UK of the health status of hypothyroid patients using T4-replacement therapy.[37] Compared to matched control patients, hypothyroid patients on "adequate" dosages of T4 had a higher reported incidence of four diseases: depression, hypertension, diabetes, and heart disease. Hypothyroid patients on inadequate T4-replacement (their TSH levels were elevated) also had a higher incidence of strokes. In addition, hypothyroid patients chronically used more prescription drugs, especially for diabetes, cardiovascular disease, and gastrointestinal conditions.

We've recently been consulted by many hypothyroid patients whose physicians have reduced their T4 dosages to extremely low amounts, in some cases as low as 25 mcg. The patients report to us that their physicians refer to reports by endocrinologists that TSH suppression increases the risk of atrial fibrillation three-fold. As I explain in Addendum 4, this is an unjustified generalization from a study of elderly (60 years of age and older) sedentary people. This misguided practice by physicians is likely to increase the patients' incidence of coronary artery disease and cardiac fatalities.

The dosage of T4 that suppresses the TSH level varies considerably, but may be as much as 171 mcg or as little as 50 mcg.[56][57][58][59][60][61][62] Hypothyroid patients should be concerned when their physicians restrict them to lower-end dosages of T4. In one study, researchers used coronary angiography to assess the progression of coronary atherosclerosis in elderly hypothyroid patients. In 5 of 6 patients who kept their T4 dosages at 150 mcg or more, the disease didn't progress. But in all 6 patients whose dosages were 100 mcg or less, the disease had progressed.[63] This study suggests that elderly patients whose TSH levels are suppressed by fairly low dosages of T4, and whose physicians insist on keeping their TSH levels within the reference range, may, as a result, have increased progression of coronary artery disease, leading to strokes and/or heart attacks. In that the incidence of atherosclerosis is high even among young individuals in modern societies, younger hypothyroid patients should be concerned over the possibility of lower dosages of thyroid hormone inducing or exacerbating atherosclerosis.

Dilemma for the Endocrinology Specialty

The four studies that are the subject of this document clearly show that neither T4- nor T4/T3-replacement is effective for many hypothyroid patients. The ineffectiveness of the two replacement therapies translates into three likely adverse consequences for these patients with inadequate thyroid hormone regulation: continued suffering from symptoms, susceptibility to potentially disabling or lethal diseases, and increased use of drugs to control the symptoms and diseases. The endocrinology specialty sets and maintains practice guidelines for the diagnosis and treatment of hypothyroidism; that it does so imposes upon it an ethical and humanitarian responsibility to expediently act to protect hypothyroid patients from the three adverse consequences. That responsibility is the compelling reason for the endocrinology specialty to promptly reform its incorrect official position that T4-replacement is safe and effective for *all* hypothyroid patients.

Many researchers, physicians, and patient advocates believe that the endocrinology specialty has been curiously obstinate in its advocacy of T4-replacement. Its obstinacy is evident in its disregard for the protests of thousands of patients and a growing number of doctors that T4-replacement is ineffective and harmful for many patients.

The specialty's obstinacy may be sustained by financial incentives from corporations that profit from the practice of T4-replacement therapy. This suspicion of financial motivation is reinforced by the specialty's standard method of enforcing the practice of T4-replacement among doctors: political tyranny rather than scientific argument and debate. The suspicion will only mount if the specialty—despite the recent studies showing replacement therapies to be ineffective[1][2][3][4] and harmful[37][63] for many hypothyroid patients—sidesteps the issue now at hand. How safe and effective is T4-replacement compared to alternate approaches to thyroid hormone therapy now in widespread use? For its own credibility, it is imperative that the specialty immediately address this issue free from prejudicial preconceptions.

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The Fibromyalgia Research Foundation
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Big Pharma Hits Pay Dirt: Fibromyalgia Patients Targeted as a Hugely-Profitable Drug Market. If you're a fibromyalgia patient, you're now targeted as a rich source of revenue from drug sales. Bookmark this page to soon read linked documents. These show the concerted efforts Big Pharma and its affiliates are devoting to you as a mother-lode of financial profit.

Sunnier Times for Fibromyalgia Patients

by Dr. John C. Lowe
Director of Research

I found the black-and-white photograph below a month or so ago, and I've gone back and peered at it over-and-over again. I've done this because to me, the image betokens the current plight of fibromyalgia patients (whom we at FRF think of as "fibromyalgia/*thyroid* patients").

Over the last twenty-five years, I've talked with countless fibromyalgia patients about their experiences with the mainstream medical system. Many of them had long accepted mainstream medicine as their only option for health care. Practically all of them ended up in frustration and despair over the failure of that system to help them. They felt that the prospects for ever recovering their health were worse than dim; their outlook seemed dark, ominous, and foreboding.

These feelings, to me, are connoted by the black underbelly of the cloud in the photograph. What has drawn me to the photo again-and-again, however, is the bright sunshine radiating around the dark side of the cloud. This sunshine symbolizes to me the hopefulness that I believe fibromyalgia patients now have reason to feel.

Fibromyalgia patients' ill feelings toward mainstream medicine are justified. That medical system for the most part offers patients only pharmaceutical drugs. But not only do the older "fibromyalgia drugs" (mainly Amitriptyline and cyclobenzaprine) fail to benefit fibromyalgia patients; the newer ones (Cymbalta, Lyrica, Savella, and all the others) benefit patients little if any better.

The failures of these drugs, however, haven't stopped Big Pharma and mainstream medicine from proffering the patients more drugs. Big Pharma has recently targeted fibromyalgia patients as a huge drug market that promises enormous financial profits. New "fibromyalgia drugs" are coming, and the FDA, thirsty for millions in fees from Big Pharma, will approve the drugs for sale. But new "fibromyalgia drugs" will work no better than the older and current ones. The reason is that they don't correct the underlying causes of patients' symptoms. As long as those causes continue to impair patients, the patients will continue to suffer from fibromyalgia symptoms, regardless of what pharmaceuticals they take.

Mainstream medicine clearly has pain-sustaining shortcomings when it comes to fibromyalgia patients. I know this is no surprise to millions of patients. What many patients may be unaware of, however, is that they no longer have to settle for the dark prospects of mainstream medicine.

I ask fibromyalgia patients to bear in mind a version of a metaphor (a trite one, I admit): that is, radiating around and beyond all dark clouds are bright, warm rays of sunshine. In the health care of fibromyalgia patients, that sunshine is scientifically-based, metabolism-normalizing natural medicine. Many fibromyalgia patients, of course, already know of nurturing radiance of this medical approach. But many others don't. Because of that, one of our new aims at FRF is to spread the word as wide and far as we possibly can.

We'll also spread the word about some new developments in health care. These give fibromyalgia patients good reason to expect to recover their health. The first development is that we've learned the main underlying mechanism of most patients' fibromyalgia. That mechanism is too little thyroid hormone regulation, due either to hypothyroidism or thyroid hormone resistance. Hypothyroidism and thyroid hormone resistance account for all of the symptoms of fibromyalgia and virtually all of the objectively verified abnormalities among patients. I want to emphasize that *no* other proposed mechanism of fibromyalgia comes even close to the inadequate thyroid hormone regulation hypothesis in accounting for what we know scientifically about the condition.

We've also learned of other underlying factors that worsen or complicate the severity of many patients' fibromyalgia. The most common of these factors are low cortisol, abnormal daytime/nighttime cortisol levels, faulty blood sugar regulation, sex hormone imbalances, pro-inflammatory diets, nutritional deficiencies, low physical fitness, and adverse effects of a variety of prescription drugs.

Clinicians Who Share Our Beliefs about Fibromyalgia Patients. The other development is the increasing numbers of clinicians who understand that fibromyalgia is a metabolic disorder.

As far as I know, the concept of fibromyalgia as a metabolic disorder due to too little thyroid hormone regulation was first proposed almost simultaneously by Professor Jean Eisinger in France and my research group. That was in the early 1990s, and at that time, we precious few others subscribed to the concept. Now, however, countless clinicians share the belief that fibromyalgia results mainly from too little thyroid hormone regulation; they also know that the patient's condition is often worsened or complicated by the other metabolism-impeding factors I listed above. These clinicians also know that integrated metabolic therapies and lifestyle practices enable most fibromyalgia/thyroid patients to recover their health. And the clinicians cooperate with patients who want to use the therapies and lifestyle practices. With so many natural or alternative medicine clinicians sharing our point view on the condition, sunshine may be shed on some 25% of the world of fibromyalgia.

Another development that fibromyalgia/thyroid patients may find interesting is the growing movement of self-treating patients. This movement arose from fibromyalgia patients' understandable frustration and impatience with the medical system. In this movement, people take full control of their own health and well-being, not leaving these to medical practitioners. They learn what they need to know, often by taking part in Internet groups of self-treating people who share with others what they've learned. And they put their knowledge to work to improve or recover their health. We at FRF praise the self-reliance of these people, and we'll do everything we can to provide information they need to better understand fibromyalgia and the methods they can use to achieve optimal health.

On this page, I've mentioned only our new educational aims, which we are vigorously pursuing. On our mission page, we've itemized our other specific new objectives, which I invite you to consider. If you feel that these objectives are worthwhile, we'll be grateful if you'll help us achieve them by contributing

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GO

Excerpt from the *Dictionary of Reality*

fi·bro·my·al·gi·a
(fī b' rō mī al' jē ə), *n.*

1. *Pathology.* widespread pain and tenderness, typically accompanied by other symptoms characteristic of hypothyroidism, usually caused mainly by a thyroid hormone deficiency or partial resistance to thyroid hormone, and often complicated by other conditions such as cortisol and sex hormone deficiencies or imbalances, a pro-inflammatory diet, nutritional deficiencies, low physical fitness, and adverse effects of prescription medications; afflicted individuals usually recover when treated with integrative metabolic therapies and lifestyle improvements, and especially when treated with thyroid hormone therapies other than replacement with T_4 or T_4/T_3.

2. *Marketing.* a medical diagnosis for a set of symptoms claimed to be of unknown origin and incurable, providing a population of medical-care consumers motivated by chronic pain to purchase a variety of prescription drugs that are largely ineffective but through media advertising and endorsements by researchers funded by Big-Pharma, provide substantial revenue for pharmaceutical corporations and the medical researchers the corporations fund.

Light is Shining on Steadily More of the World of Fibromyalgia

Many natural or alternative medicine clinicians now share FRF's point of view point on fibromyalgia.

Our viewpoint is that fibromyalgia is a metabolic disorder, and afflicted patients require metabolic treatment and lifestyle changes that improve metabolism. The most important metabolic treatment for most patients is thyroid hormone therapy *other than T4 or T4/T3 replacement.* Thyroid hormone replacement (with dose adjustments that keep the TSH within its current-but-often-changing reference-range) is *not* effective, according to studies, for some 50% of patients.

In that today, many clinicians share our point of view, most fibromyalgia patients can recover their health. To accomplish that, they must find natural medicine clinicians, to FRF. Donations to FRF are tax-deductible. Also, after you read about our new objectives, if you have any suggestions or questions, we'll be happy to hear from you. All best wishes to you from the whole FRF team.

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alternative medicine clinicians, complementary medicine clinicians, or what ever one wants to call these more effective clinicians. The patients must them work with the clinicians to improve or hopefully fully recover their health.

If you cannot find a cooperative clinician, don't despair. You still have the option of *self-guidance* to recovery. We at FRF now enthusiastically advocate the self-care approach for fibromyalgia/thyroid patients.

Support of the movement of patient-self-care isn't new. In his early 1989 book titled *Chronic Muscle Pain Syndrome* (Berkley Books, New York, pages 12-13), rheumatologist Dr. Paul Davidson praised the self-care movement.

Dr. Davidson wrote, ". . . enough is known about fibrositis (termed "fibromyalgia" since late 1989) to permit effective *self*-treatment to some extent . . ." (Italics ours).

Dr. Davidson also wrote, "Self-treatment has no small significance in this age of enormous medical costs. Whatever suffers can do to participate in their own treatment represents a great source of self-satisfaction and a saving of consumer dollars."

It's worth noting that Dr. Davidson was aware in 1989 that enough was known about fibromyalgia. ". . . to permit highly effective treatment in most cases." He was referring to treatment by clinicians, and he was right—enough was know at that time to effectively treat most patients. Some ten-years later, however, high-profile rheumatologists who studied fibromyalgia admitted publicly that they had never gotten a fibromyalgia well. These same rheumatologists, to this day, steadfastly refuse to consider that fibromyalgia can be a symptom patter that results from hypothyroidism or thyroid hormone resistance. Until they do, they'll have continue their record of failing to help fibromyalgia patients recover their health.

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Biography of Dr. John L. Gedye

Director in Memoriam
Fibromyalgia Research Foundation

In Memory of Dr. John L. Gedye

- B.A., Part II Natural Sciences Tripos (Psychology), University of Cambridge, 1954.

- M.B., B.Chir. degrees, (equivalent of American M.D.) University of Cambridge, 1957.

- House appointments in Academic Units of Medicine and Surgery, University of Cambridge College Hospital, London, 1957-1959.

- Formerly, Squadron Leader, Royal Air Force Medical Branch and Junior Specialist in Aviation Physiology, Royal Air Force Institute of Aviation Medicine, Farnborough, England, 1959-1964

- University Lecturer in Psychopathology, and Director of Unit for Research on Medical Applications of Psychology, University of Cambridge, Cambridge, England, 1964-1968.

- Fellow, Lecturer, and Senior Lecturer and Director of Man-Machine Systems Laboratory, Department of Electrical Engineering Science, School of Physical Sciences, University of Essex, Colchester, England, 1968-1975.

- Research Associate Professor of Neurology, Baylor College of Medicine, Houston, Texas, 1975-1977.

- Professor of Neurology, School of Medicine, and Adjunct Professor of Electrical and Computer Engineering, College of Engineering, Wayne State University, Detroit, Michigan, 1977-1980.

- Consulting business: multi-user (UNIX) computing systems for professional applications, 1980-1996.

- Associate Director for Clinical Research, Parker College of Chiropractic, Dallas, Texas, 1996-1998.

- Board of Directors, Fibromyalgia Research Foundation, 2000-2002.

- Director, In Memoriam, Fibromyalgia Research Foundation, 2002 . . . .

In Memory of Dr. John L. Gedye

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In Memory of John L. Gedye, M.B., B.Chir.

December 25, 1932—June 28, 2002

Dr. John C. Lowe
June 29, 2002

Biography of Dr. John L. Gedye

Last night I received an e-mail from Frank Lucatelli, best friend of Dr. John L. Gedye, addressed to Dr. Gedye's friends and colleagues. Frank wrote:

> "My dear friend John L. Gedye left this world for the next this morning, Friday, June 28, 2002 at 10:54 AM while at Beaumount Hospital in Detroit, MI. His passing leaves an empty place behind that few can fill. Anyone who has had the opportunity to experience the keen intellect and caring spirit of this man knows what I mean. He will be greatly missed."

For the rest of the evening, after reading Frank's e-mail, I felt numb and detached. I think this state of mind was a self-protective mode. John Gedye was dear to me, and for several reasons, his death is a painful loss. Before becoming fully conscious of the loss, some benevolent internal device allowed me time to position myself to absorb the staggering blow—the second in a short time. The first came some two months ago when one of the most important people in my life passed on.

Today, what brought me to squarely face John's death was the obvious distress of Dr. Gina Honeyman. She feels a strong emotional bond with John, and his absence is painful to her. Their emotional bond formed when John stayed with us in Tulsa, Oklahoma for several days in late 1999. At lunch one day, John told her of his experiences as a young boy during the German air bombing of England. While telling the story, he cried, and she learned of the deep compassion he felt for other human beings and the pain he suffered over the misfortunes of others. The bond Gina felt with John was solidified, I think, at a meeting of alternative doctors in St. Louis we attended in early 2000. At the meeting, Frank Lucatelli and John became tearful in front of the audience of doctors. They had been talking of their diligent work to form an organization of practitioners who had developed promising clinical approaches but were largely blocked from providing them by the good-ol'-boy system of mainstream medicine. It appeared to me that Frank and John's passion for this mission, and its meaning for the relief of human suffering, overwhelmed them and made them tearful, despite the public circumstance. My enormous respect and affection for John are based partly on what these emotional moments represent: They highlight the emotional underpinnings of his concern for suffering humans. This concern drove his persistence to bring together clinicians and scientists with overlapping interests so that the word about promising, innovative approaches to patient care could spread.

My impression of what's so upsetting for Gina today is that she's had time to ponder what she felt for John. He was an extraordinary person for whom she cared a great deal, and the thought of not communicating with him again disturbs her deeply. She commented that in this modern life, we run so relentlessly trying to put out brush fire after brush fire that we end up reserving too little time for the people we care about and value; then, when one of them is suddenly gone, we realize our failure to have spent our time wisely.

Aside from her own emotional bond with John, Gina is also upset over the loss of John from my life. As she said, he was possibly the only physician—other than she—who has truly understood what my work is about, its true quality from the standpoint of science and logic, and what our research has actually shown. She and I are painfully aware that now, we'll no longer have the occasional uplifting experience of understanding, appreciation, and acceptance by this human being whose judgment was so extraordinarily sound.

Gina is right. John was the rare scientific mind among his medical colleagues. Before becoming a physician, he had been educated as a behavioral psychologist, as was I. Behavioral psychology in those days was far more scientific than medicine has ever been. And most physicians who've had the advantage of being educated first in behavioral psychology are conspicuous for their superior understanding of science and their relative exemption from the intellectual shortcomings of most other physicians. John's and my common background in behavioral psychology and its intellectual benefits formed a bond between us.

John and I first met when he sent me an e-mail in 1996 asking what I thought of Dr. Dennis Wilson's ideas. I wrote back explaining my objections to most of Wilson's beliefs, and afterward, he and I occasionally exchanged e-mails. From these communications, it was clear to me that John had immense intellectual stature, and I found the British color of his written thoughts delightful.

John and I finally met in person in May of 1998. The place was the University of Texas, Health Science Center, in Houston. He and I were participants there in the First Congress on Defining a New Paradigm for the Healing Arts. The Congress was the brainchild of a courageous, iconoclastic physician named Dr. Richard Garrison, then with the Department of Family Medicine and Community Health. At the time, I was ill with an over-work-induced head cold, but I enthusiastically participated in the Congress, accompanied by my dear friend, longtime editor, and research colleague, Jackie Yellin. While I wanted to have my say at the Congress, my main purpose in attending was to meet in person the distinguished intellectuals who were to attend. These included Dean Black, Ph.D., John Diamond, M.D., and above all, John L. Gedye, M.B., B.Chir.

I formed a strong affinity for John at the Congress. This occurred when I learned of his response to my presentation of my main method for pursuing truth about the nature of fibromyalgia and its treatment: formal logic. Both John and physicist Elizabeth Rauscher (another participant in the Congress) appreciated the crucial role of formal logic in the pursuit of scientific truth. Elizabeth's appreciation was primed by her having taught philosophy of science—of which formal logic is an indispensable part—as a university professor. John's appreciation came first from his background in behavioral psychology, which had given him a practical understanding of science. More so, though, his appreciation of formal logic was based on the product of his colossal intellectual thirst. That product was an astonishingly vast and thoroughgoing knowledge of the nature and philosophy of science, as well as the principles and practice of logic. Such knowledge is rare among human beings in general, and in my judgment, almost nonexistent among other physicians *including those most prominently involved in medical research*. John and I occasionally lamented that the ignorance of science philosophy and logic among medical researchers—including those at the National Institutes of Health and the CDC in the USA, and the equivalent institutions in the UK—is one of the main reasons that so-called medical "science" provides the public with paltry returns for the scores of billions of invested taxpayer dollars devoted each year.

After the Congress, John and I became friends and communicated often by e-mail and telephone. We occasionally did one another favors that I believe betokened our friendship. For example, when I was struggling to finish *The Metabolic Treatment of Fibromyalgia*, I was so stressed, exhausted, and mentally depleted that my health began to fail. A disturbing development was what seemed to be a lump in my throat. The "lump" was prominent and showed itself with every swallow. I became convinced that a cancerous tumor in my esophagus was probable. John generously spent time calming my apprehension. He explained that in England, he'd once worked as a physician in a clinic for the diagnosis and treatment of diseases of the esophagus. While not discounting my concerns, he explained that the vast majority of patients evaluated at the clinic had stress-induced symptoms of the esophagus, and he speculated that the extreme stress I was under could very well have induced a persistent esophageal spasm that I was experiencing as a lump in my throat. He told me that the treatment that effectively relieved the symptoms for the vast majority of patients at the clinic had been stress-relieving psychological therapies. Just to be sure, however, my wife took me for evaluation at the radiological center where she often ordered imaging procedures. There, a radiologist found no evidence of a physical lesion in my esophagus. I then acted on John's sage and patient counsel, and cured the "lump" in my throat through stress-relieving methods.

To illustrate how I felt about John over the years and still do, I'll mention a favor I did for him in August of 1998. John was interested in starting a new journal. John's friend Frank Lucatelli and Annamarie White, who had done technical writing for the Smithsonian, would also be taking part in publishing the journal. I suggested that John propose the new journal to a successful medical publisher I knew, Bill Cohen, and I wrote Bill a letter introducing John. Below are excerpts from the letter containing comments on some of John's fine qualities.

> **Dear Bill:** The purpose of this letter is to introduce you to Dr. John L. Gedye. He'll be contacting you soon to propose

> a new journal. I suggested to him that I communicate with you beforehand in the way of an introduction. I wanted to do this because I find Dr. Gedye quite an extraordinary man, and I know that I'm not alone in this perception of him.
>
> I mentioned to you a month ago in another letter that I'd taken part in the Houston Congress for Defining a New Paradigm for the Healing Arts. For a month before the actual Congress, extensive Internet communications took place between some of us who would attend and participate in the Congress. Dr. Gedye was the most prolific of those who participated in the pre-Congress Internet postings. In looking back over these postings (which were printed and handed out at the Congress), I'm most appreciative of the volume of his postings because of the high quality of the scholarly thoughts he expressed in them. I was very busy with other matters during the Internet communications, and early on, I didn't read many of the postings. My wife (Dr. Gina Honeyman-Lowe), however, read most of them from the beginning. It was she who brought my attention to Dr. Gedye's posts. She was most impressed by them and enthusiastically checked her e-mail each day to see if he'd written more. I took up the same practice after taking time to read all his posted communications.
>
> When I went to the Congress in Houston, one of my main interests was to meet Dr. Gedye in person. I found him to be a refreshing combination of scientific astuteness and congeniality. He's one of the precious few researchers I've met who is well versed in science philosophy and logic—intellectual tools that are requisite to effectively solving problems through research. I've learned that Dr. Gedye truly practices, whether through instinct or intellectual volition, what every great philosopher of science has declared: that when confronted with new ideas, we should clear our minds of judgments based on preconceived beliefs, welcome the ideas, accept them for scientific consideration, and reject them only if they don't hold up to scrutiny by applied logic and empirical testing. I believe there's a virtual absence of this practice among modern medical researchers. I also believe this absence is one of the fundamental obstacles to progress through medical research, and one of the reasons why the current medical paradigm shows distinct signs of crumbling. Dr. Gedye's practice of this necessary step in truth-seeking and problem-solving makes him perfectly suited to head up the journal he'll propose. In addition, his open-mindedness and congeniality have mustered support from like-minded individuals in diverse fields of health care and science. I'm confident that they, as I, will enthusiastically support the journal Dr. Gedye will propose.
>
> My wife and I have had the privilege of spending time with Dr. Gedye. We've been very much impressed with the qualities we have seen in him. We've found him to be gracious, compassionate, tolerant of divergent views, highly literate, and an unusually stimulating conversationalist. As I said at the beginning of this letter, Dr. Gedye is quite an extraordinary man. I am confident that you'll enjoy meeting and communicating with him.

In addition to gestures of friendship between John and me, I enjoyed a bountifully rewarding communicative relationship with him. For the most part, I queried him and listened and absorbed his opinions and views; I enriched myself at his expense. On the other hand, and to my delight, his extensively expressing himself in his eloquent, diplomatic British tongue was an activity to which he wasn't particularly averse. Never have I known another human whose intellectual interests and inclinations so closely overlapped mine, and yet were so much more developed than mine that the relationship nourished my mind. My work had given me specialized knowledge in a field in which John wasn't expert. Yet his greater breadth and depth of knowledge in the fields that undergird my scientific work left me feeling that the balance of benefits in our relationship was tipped in my favor in a way that I wasn't equipped to rectify.

I'm so proud that John wrote the Foreword to my book *The Metabolic Treatment of Fibromyalgia*. In January of 2000, I recommended to the Board of Directors of the Fibromyalgia Research Foundation that John be appointed to the Board. I did so for several reasons: my admiration of his emotional commitment to humanitarian concerns, his exceptional knowledge of science and logic, and his expertise in the practicalities of research. The Board enthusiastically welcomed him, and he served as a Director until his death. John is now, and will remain, a posthumous member of our Board. In our upcoming studies, the absence of the conceptual and technical contributions he would have made will truly be sorely felt.

With John's passing, one of my richest intellectual resources is gone. Now, at least for a while, I feel much like a sail hanging limp because the wind suddenly left it. Perhaps the impact of John's death would be somewhat less had I not, only two months ago, lost my greatest literary inspiration with the death of my beloved nephew Brian Bain. Brian was a genuine, born genius of the English language. His presence in my life was a gift, not only because I loved him, felt pride in him, and had great joy because of him, but also because his prodigious, awe-inspiring use of the English language moved me to do my best, in my pedestrian way, at using that same language. In regard to science, logic, and compassion toward suffering humanity, John Gedye moved me in a similar way. Now, bereft of these rare human sources of inspiration, I must depend on my memories of them and their marvelous ability to inspire.

I read somewhere that we never really appreciate a resource until we've lost it. This generalization doesn't apply to my appreciation of John Gedye. While he was here, I valued him greatly as part of my life, and I was well aware of how he enriched it. I wouldn't change my full awareness of how special a man he was, although undoubtedly, it intensifies the sorrow I feel at his absence.

I've allowed myself a measure of self-indulgence in these comments, and now wish to place them into the proper context. They do, after all, have a purpose beyond my own catharsis. It has been said that those who've left us have but one chance at immortality. That chance lies in what they've left behind: our memory of them. The impact of a person's life, the effect that life had on other people, their experience of the person—this is what remains. We honor John Gedye by remembering, and continuing to remember, how he affected us and why we'll miss him so much.

Biography of Dr. John L. Gedye

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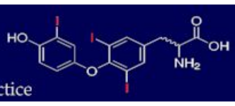

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TSH is Not the Answer: Rationale for a New Paradigm to Evaluate and Treat Hypothyroidism, Particularly Associated with Weight Loss

(Full Text Free in pdf format)

Carol N. Rowsemitt, PhD, RN, FNP and Thomas Najarian, MD

Correspondence: Dr. Carol Rowsemitt, San Luis Obispo, CA, rosey805@gmail.com
Correspondence: Dr. Thomas Najarian, Incline Village, NV, tnajarianmd@hotmail.com

Abstract. While many endocrinologists continue to debate the appropriate levels of TSH to use as boundaries for normal limits, we believe using TSH to assess thyroid function is counterproductive, particularly in those patients attempting to lose weight. From the published literature and our own clinical experience, we have come to understand that the set point for metabolism is adjusted downward in the hypocaloric state. The decrease in metabolism is often referred to as part of the “famine response.” This metabolic response has been documented in several major vertebrate classes demonstrating its widespread importance in nature. In our current environment, the famine response limits the patient’s ability to lose weight while consuming a hypocaloric diet and performing modest levels of exercise. Our own experience with the famine response is consistent with that found in the literature. Treating to normalize thyroid hormone levels and eliminate hypothyroid symptoms results in the suppression of TSH. This is understood as a normal part of treatment once we accept that the thyroid set point has been lowered. This is not an argument to use thyroid hormones to increase metabolism above normal to achieve weight loss. Our goal is to correct the hypothyroid response in a weight loss patient and return him/her to normal metabolism so that the patient feels normal and is better able to lose weight and maintain that loss.

Keywords • Famine response • Hypocaloric state • Hypothyroidism • Reverse triiodothyronine • rT3 • T3 • TSH • Triiodothyronine

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Written responses to Dr. Najarian and Dr. Rowsemitt's two papers published in *Thyroid Science*.

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Hypotheses

TSH is Not the Answer: Rationale for a New Paradigm to Evaluate and Treat Hypothyroidism, Particularly Associated with Weight Loss

Carol N. Rowsemitt, PhD, RN, FNP and Thomas Najarian, MD

Correspondence: Dr. Carol Rowsemitt, San Luis Obispo, CA, rosey805@gmail.com
Correspondence: Dr. Thomas Najarian, Incline Village, NV, tnajarianmd@hotmail.com

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Abstract. While many endocrinologists continue to debate the appropriate levels of TSH to use as boundaries for normal limits, we believe using TSH to assess thyroid function is counterproductive, particularly in those patients attempting to lose weight. From the published literature and our own clinical experience, we have come to understand that the set point for metabolism is adjusted downward in the hypocaloric state. The decrease in metabolism is often referred to as part of the "famine response." This metabolic response has been documented in several major vertebrate classes demonstrating its widespread importance in nature. In our current environment, the famine response limits the patient's ability to lose weight while consuming a hypocaloric diet and performing modest levels of exercise. Our own experience with the famine response is consistent with that found in the literature. Treating to normalize thyroid hormone levels and eliminate hypothyroid symptoms results in the suppression of TSH. This is understood as a normal part of treatment once we accept that the thyroid set point has been lowered. This is not an argument to use thyroid hormones to increase metabolism above normal to achieve weight loss. Our goal is to correct the hypothyroid response in a weight loss patient and return him/her to normal metabolism so that the patient feels normal and is better able to lose weight and maintain that loss.

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Introduction

Major controversies regarding appropriate thyroid treatments are ongoing and are affecting the morbidity and most likely mortality in many populations. In his 2008 paper, Dommisse has extensively covered the disagreements in this area and presented arguments which challenge the views of the majority of the medical community.[1] While we agree with him, we bring a unique experience base to the discussion which, we believe, supports and adds to Dommisse's work.

The authors have the clinical experience over the past eight years of treating over 15,000 obese patients with a healthy low carbohydrate, low fat diet, supplements to correct any nutritional deficits from the low calorie diet, a program of light exercise, and various medications for appetite control used both on and off label. The weight loss in our clinic has averaged about 19% at 2 years for those who stay on treatment that long. Other benefits that we have observed with this treatment are improved blood pressure using fewer antihypertensive medications, improved glycemia, again with fewer anti-diabetic medications, improved lipids, and improved quality of life.

When using these highly effective appetite suppressants on our obese and overweight patients, we have found approximately one third of them suffer the common phenomenon of reaching a plateau while continuing our diet and exercise recommendations. These patients have accompanying symptoms of low thyroid which may include coldness, cold extremities, fatigue, joint aches, hair loss, constipation, and depression. Our clinical experiences have led us to believe that the inappropriate assessment of thyroid function using thyroid stimulating hormone (TSH) is an important factor contributing to the inability of many patients to lose weight and maintain the loss. TSH is considered the gold standard for evaluating thyroid function because it responds in logarithmic fashion to subtle changes in thyroid hormone levels, decreasing dramatically in the circulation when thyroid hormone levels rise and increasing dramatically when they drop.

Thus, it would appear that the portions of the brain involved in metabolism are using this pathway to tightly defend a homeostatic level. While we certainly agree that this pathway is used, we will demonstrate that there are times when providers must choose to override the homeostatic set point and treat based on other available indicators of metabolism. The paradigm we are proposing shifts away from using TSH to assess medically appropriate treatment of hypothyroidism once this phenomenon is understood using a more global view of negative feedback systems in animals. Arguments about the appropriate range for normal TSH are rendered irrelevant by our view.

Much of what we will argue is already in the scientific literature but is unknown, not understood, or not accepted by most prescribers. These concepts apply both to hypothyroid patients already on thyroid treatment as well as those who are normal in both thyroid hormone levels and metabolism prior to attempting to lose weight.

1. The homeostatic set point for metabolism (mediated via thyroid hormones) is reset at a lower level in the hypocaloric state in some patients. The resultant lowered energy expenditure may be highly adaptive when food is scarce; but it hinders weight loss attempts in our obese and overweight patients. These patients may also suffer from symptoms of low thyroid such as coldness, cold extremities, fatigue, joint aches, hair loss, constipation, and depression.

2. The health care community is well aware of the concept of homeostasis but does not consider the well-studied concept of alterations of set points.

3. During weight loss attempts, when thyroid is carefully replaced to eliminate hypothyroid symptoms and restore normal circulating levels of thyroid hormones (free triiodothyronine [FT_3] and free thyroxine [FT_4]), TSH is suppressed (personal observation).

4. This suppression of TSH should be understood to represent part of the normal feedback mechanism by which the body decreases metabolism to maintain stored resources in the face of insufficient nutrition. This level of TSH should not be used to regulate thyroid dosing. If a provider regulates thyroid hormone dosing based on TSH in these circumstances, the patient's weight loss attempt will be severely hindered.

5. Reverse T_3 (rT_3), which increases in the famine state, may have a function in suppressing metabolism in humans.

6. We will critique arguments against thyroid treatment in the hypocaloric state.

7. Once the relative importance of TSH versus FT_3, FT_4, and rT_3 are reconsidered in the hypocaloric condition, it is appropriate to carry this argument to the non-dieter.

Given the critical nature of the obesity epidemic, we feel it is time to express these ideas in a thorough manner in hopes that providers will begin to work on bringing the patient's metabolism back to normal during weight loss attempts. Further, even in the non-dieting patient, evaluating symptoms, FT_3, FT_4, and reverse T_3 are of more value than TSH for improving patients' quality of life.

1. Resetting the Thyroid Hormone Set-Point: "The Famine Response"

Many studies have reported changes in metabolism in the hypocaloric state in humans. Early literature was reviewed in the seminal work of Keys et al.[2] in their experimental study of human starvation. Our own coverage of the literature is summarized in the Table. (This table is not designed as an exhaustive literature review, but rather to provide the reader an overview of the general findings in this field. We also provide limited information regarding details other than hormone blood levels. Again this is merely to provide the reader with a concept of what else has been studied.)

Almost without exception, experimental studies of fasting or low caloric intake in humans show decreases in circulating levels of total T_3 (TT_3) (all of the 22 studies) and FT_3 (all of the eight studies) with increases in rT_3 (16 of 17 studies). (There are two alternate pathways for T_4 metabolism: to the active hormone (T_3) or to rT_3. Most providers believe rT_3 is an inactive byproduct.) T_4 results are mixed.

For total T_4 (TT_4), four studies show increases, 10 no change, and four show decreases. Similarly, for FT_4, seven show increases, 4 no change, and one shows a decrease. The results for TSH are mixed, showing either decreases (six studies) or no changes (nine studies), but never an increase.

There are also a limited number of reports of other relevant variables in humans and laboratory rats (Table). These hormonal changes are similar to those found in euthyroid-sick syndrome[3] and, in fact,

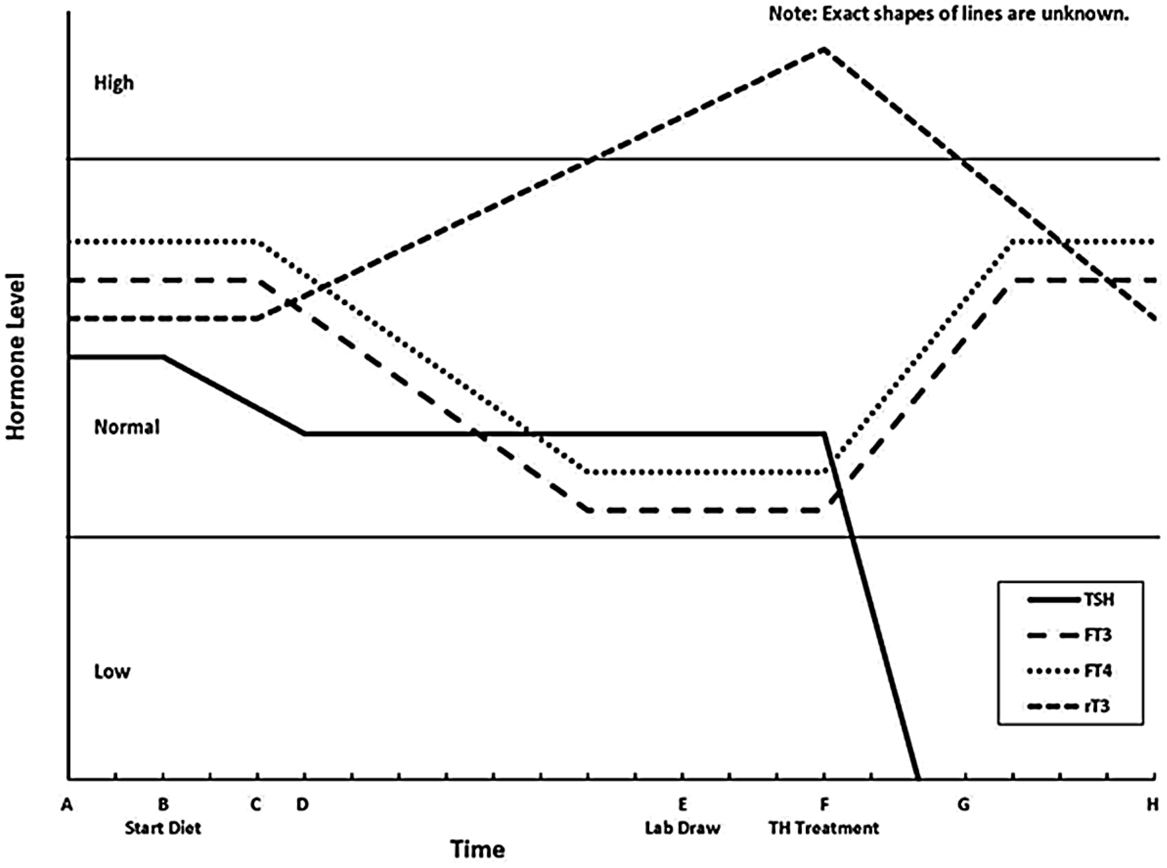

Figure. Hormonal responses to a hypocaloric state with subsequent treatment. Note: Time frames and shapes of response curves are unknown. Levels of all four hormones are normal before the diet (Time A). At time between time points B and D, TSH is dropping slightly to signal the thyroid gland to make less thyroid hormone. This drop is the mechanism to decrease metabolism in the hypocaloric state. At point C, free T_3 begins to drop as rT_3 increases. Also at time point C, different observations have been reported for changes in FT_4: in our experience, FT_4 also drops as indicated on the graph. In the literature, some report no change, whereas others report an increase in FT_4. By the time of the blood sampling (time E), in our experience, patients whose FT_3 and FT_4 have dropped to the low end of normal (with possible above normal rT_3 levels) are those experiencing symptoms of low thyroid. They may have any of the following symptoms: feeling cold, cold hands and feet, elevated diastolic blood pressure secondary to vasoconstriction, fatigue, depression, constipation, hair loss, dry skin, insomnia, as well as others. They have often hit a plateau of weight loss even though they have continued to maintain their hypocaloric diet and exercise program. At point F, we begin treatment with thyroid hormone (T_4 with T_3, T_3 alone, or desiccated thyroid, depending on the situation). Between points F and G, FT_3 and rT_3 (and FT_4 if it was administered) are returning to more normal levels, while TSH plummets, often to undetectable levels. At time point H, symptoms of low thyroid are resolved, the patient has no symptoms of hyperthyroidism, and if rT_3 had risen and was treated appropriately, rT_3 decreased.

the hypocaloric state has been used as a model to study these hormonal changes in severe illness. Our figure demonstrates these changes graphically.

Unfortunately, the famine response escapes detection by current laboratory evaluation of the thyroid. In our clinical experience, the differences found do not reach levels one observes in pathological states. Before dieting (Figure: times A – B) TSH, free T_4, and free T_3 are within normal limits. After dieting starts (times B – F), decreases occur in these three hormones in many patients, but the hormones remain within normal limits. Furthermore, clinicians are looking for an increase in TSH to indicate a decrease in thyroid function, not a decrease in TSH. And the decrease that occurs is not enough to be noticeable on an individual clinical laboratory assessment. Only when data are available before and during a hypocaloric treatment can these differences be observed (Table).

Thus, when a patient presents with symptoms of low thyroid and is unable to lose weight despite serious caloric limitation, most clinicians test for primary hypothyroidism with a TSH assay. The likely result is a TSH at the lower end of normal (Figure: times D – F). The clinician interprets the TSH reading to mean that the thyroid hormones are within normal limits and, if anything, to assume that FT_3 and FT_4 are on the high end of normal. If the patient requests a FT_3 and FT_4, those are likely to be at the low end of normal or only slightly below normal (personal observation, TN and CR). The provider would be likely to conclude that there is nothing wrong with the patient's thyroid function despite the symptoms. The patient is often told to get more exercise and that s/he must be eating more calories than realized.

We would agree that there is nothing "wrong" with the patient's thyroid function. The hypothalamic-pituitary-thyroid (HPT) axis is performing in a highly evolved manner to help the patient live through the current caloric limitations. In the clinical setting, one is unlikely to have the comparison of pre-famine to famine hormone levels as has been documented in clinical research studies. The results of these studies conflict with our understanding of normal adult human homeostasis. Under our usual understanding of human endocrinology, we would not expect a decrease in FT_3 or FT_4 to occur simultaneously with a decrease in TSH. Rather, we would expect a decrease in FT_3 or FT_4 to be met by an increase in TSH as the feedback loop's mechanisms work to achieve maintenance of a stable set point.

2. But Is It Not Unusual to Alter a Homeostatic Set Point?

Actually, it is not unusual for set points to change. However, homeostasis is a major paradigm providing the framework for our learning of much of human physiology and endocrinology. This concept is generally the first idea taught in introductory human physiology class. We are not taught to think of humans as having set point changes except for the well-recognized differences in reproductive hormone levels before and after puberty. The concentrations of androgens and estrogens are regulated at low levels before puberty. An important way to think about this is that low concentrations of the reproductive steroids are sufficient to suppress production of GnRH, LH, and FSH during childhood, whereas much higher levels of these steroids are required to inhibit the relevant hypothalamic and pituitary hormones after puberty. By definition, this means that the hypothalamic and pituitary set points change during maturation. After puberty, these sites are much less sensitive to the gonadal steroids.

Broadening our view to include eco-physiological adaptations of other animals demonstrates obvious changes in set points. Body temperature set point alterations in hibernating mammals are well studied. Hibernating mammals do not simply allow body temperature to drop to ambient temperature; e.g., a hibernating bat will maintain a body temperature slightly above ambient.[4] Hummingbirds, which maintain a very high metabolic rate during the day, go into torpor [a dormant state of low metabolism] at night, resetting their temperature set point to produce a much lower metabolic rate during their inactive time.[5]

Probably the best studied change in set point is that occurring in seasonal breeders. Extensive studies of long-day breeders (rodents) and short-day breeders (sheep) have elucidated mechanisms in which feedback set points are seasonally reversible. See Bronson[6] for review. Males maintain large testes and high circulating testosterone levels during the breeding season; during the non-breeding season, testes regress and testosterone levels may be almost non-detectable. In mammals, the control of these variations by day length is well known. Seasonal decreases in mass and functioning of gonadal and accessory tissues are understood to be adaptations to minimize androgen-dependent energy expenses during the non-breeding season (e.g., mate-seeking, aggression, and maintenance of testes and accessory organs). Such hormonal differences could not be produced and maintained if the set point of the feedback for testosterone remained constant.

Seasonal and facultative responses are not so obvious for humans living with regulated household temperature, warm clothing for cold weather, and constantly abundant food. We are so buffered from the vicissitudes of the environment that it is easy for us to view modern adult *Homo sapiens* as being in a single homeostatic state rather than considering our own species as having the ability to adapt to altered environmental conditions. For many circumstances, this view is adequate for our understanding of human systems. However, by considering ecological factors, we can sometimes increase our understanding of human physiological issues. The identification of seasonal affective disorder (SAD) approximately 25 years ago demonstrated a strong connection to seasonal day length changes in a subset of the population. SAD is now widely accepted as a disorder which can be treated with phototherapy.[7]

In light of this understanding of adaptive physiological responses in humans and a variety of other vertebrates, we can now view hypocaloric patients differently. Almost without exception, studies show that decreased caloric intake in humans caused decreased circulating levels of TT_3 and FT_3 with increased rT_3 (Table 1). These individuals are using the famine response to stay alive when food resources are inadequate. Similar responses have been reported in several vertebrates, including desert tortoises,[8] herring gulls,[9] and mink.[10] For review, see Eales, 1988.[11] The widespread nature of this response is explained either by its appearance prior to the evolution of these distinct vertebrate classes or its independent evolution many times. In either case, its importance becomes obvious.

For the patient in the hypocaloric state, we must now re-evaluate how we view the hypothalamic-pituitary-thyroid (HPT) axis. This complicates the question of the appropriate evaluation and treatment of thyroid dysfunction. Subtle decreases in TSH and borderline low values of free T_3 and/or free T_4 with increases in rT_3 are indicative of a low-metabolism state that inhibits desired weight loss. The famine response can be viewed as maladaptive in our current obese and overweight patients attempting to lose weight. While the adipocyte hormone leptin plays an important role in regulating thyroid hormones and other aspect of the famine response (Rosenbaum and Leibel for review),[12] our own work focuses on the thyroid portion as this can be treated currently and has shown profound effects for many of our patients.

3. In the Hypocaloric State, Treatment of Low Thyroid to Produce Normal Levels of FT_3 or Both FT_3 and FT_4 Results in Suppression of TSH without Symptoms of Hyperthyroidism

We have observed this phenomenon in our patients over the years: administration of both T_3 and T_4 to produce normal serum levels of both hormones causes suppression of TSH (Figure: times F – H). If only T_3 is administered, T_3 levels are normalized and TSH is suppressed. When FT_3 alone or both FT_3 and FT_4 are corrected, clinical symptoms of hypothyroidism are resolved.

Proof that this phenomenon represents a change in thyroid homeostatic set point is that, by definition, a deviation from the set point of circulating thyroid hormones will cause a change in TSH in response. When experimental subjects are given T_3 to eliminate famine-induced hypothyroid symptoms, TSH is suppressed with no symptoms of hyperthyroidism.[13-15]

4. Suppression of TSH Either in the Hypocaloric State or in a Non-dieting Hypothyroid Patient Treated to Optimize Well-being Should be Understood to Represent the Body's Response to its Altered Set-Point for Thyroid Feedback

This is most easily explained as we do for patients: *Your body has chosen to decrease metabolism (by decreasing thyroid hormone levels) to save your life in this time of limited resources. The fatigue and coldness you feel are the body's attempt to make you burn fewer calories by decreasing your optional activity and lowering the heat generated.* (When asked, patients realize that they do not shiver or horripilate [develop "goose bumps"] during these times of extreme coldness. This demonstrates that the body is not attempting to correct the coldness with its usual autonomic responses: increasing heat production [shivering] or attempting to save heat [horripilation].) *When we bring your metabolism back to normal by giving you thyroid hormones to produce normal circulating levels, your body's regulatory systems assess this as a higher metabolic rate than the body wants for the low calorie state. Your brain thinks your thyroid must be making more thyroid hormone than is appropriate, i.e., parts of the brain are saying, "I'll die of starvation if I maintain normal metabolism. I need to decrease thyroid hormone production and I do that by not making TSH; this allows my thyroid hormones to drop back to lower levels." So TSH can go to zero while the body attempts to bring thyroid hormone levels and metabolism back down to their new, energy-conserving levels. Since we are providing exogenous thyroid hormone, this presents a challenge for the body.* In terms of symptoms, the patient now feels normal without either the previous hypothyroid symptoms or any symptoms of hyperthyroidism. (See figure for a graphic explanation.)

In cases like this, the primary care provider often receives a laboratory report of a suppressed TSH and informs the patient that his/her thyroid is being over-treated and that s/he should stop the thyroid treatment. The provider ignores the information that FT_3 and FT_4 are within normal limits and that the patient has finally ceased having symptoms of hypothyroidism and has started to lose weight again.

5. Reverse T_3 May be Part of the Mechanism Suppressing Metabolism in Humans

While most clinicians believe that rT_3 is a waste product and merely a pathway the body uses for the elimination of T_4, the literature provides arguments for a role for rT_3. Changes in kidney function show intriguing results. In fasting, tubular reabsorption of T_4 and T_3 is decreased[16] whereas that of rT_3 is increased.[17] Such variation in kidney function suggests that manipulation of plasma levels of these components is being performed based on caloric intake. While we find it difficult to understand the rationale for Wilson's specific approach to treating high rT_3,[18] we can see the general logic of a role for rT_3 in decreasing metabolism since rT_3 is known to compete with both T_3 and T_4 for transporters and receptors.[19] rT_3 also inactivates and degrades D2, the enzyme which both converts T_4 to T_3 and degrades rT_3.[20,pp.50,54] rT_3 also decreases the activity of D1, another enzyme involved in the same two pathways.[20,p.54]

So in a hypocaloric state, there is a relatively higher concentration of rT_3 and lower concentrations of both T_3 and T_4; also the available rT_3 can inhibit the functions of T_3 and T_4. All of this suggests a role for rT_3 in decreasing metabolism.

6. Critique of Arguments against Thyroid Treatment in the Hypocaloric State

It would appear obvious to attempt to replace the decrement in thyroid hormone levels to return metabolism to normal in patients in a weight loss program. However, several issues have prevented the medical community from pursuing such treatments.

Misdiagnosis of Hyperthyroidism. Extensive literature has addressed the question of side effects of hyperthyroidism. In some cases, clinicians have diagnosed hyperthyroidism because of a suppressed TSH, without assessment of symptoms or FT_3 and/or FT_4 levels.

Osteoporosis Risk. There are many reports of increased risk of bone loss with thyroid replacement for post-thyroid cancer patients. Most of these reports focused on suppressed TSH. In a non-famine state, TSH suppression generally indicates high thyroid hormones. However, as the ideas presented here demonstrate, the hypocaloric state causes a decrease in TSH without FT_4 and FT_3 being above normal limits. In this extensive body of work showing that TSH suppression decreases bone mass, FT_4 and/or FT_3 levels are not presented.

In an account where the actual thyroid hormones are maintained within normal limits and calcium supplements are provided, osteoporosis is not a problem.[21] Our patients who have had routine bone scans have not seen diminution of their bone density. Others anecdotally report the same.[1] In one osteoporosis clinic, thyroid treatment is evaluated by symptoms and thyroid hormone levels. Often, TSH is suppressed to achieve optimal functioning. Bone loss has not been a problem. (M. Gonzalez, MD, personal communication.) A recent review[22, pp. 684-686, 696] covers literature demonstrating inconsistent conclusions of reviews and meta-analyses of thyroid effects on bone density. The authors suggest that most of the study interpretations are confounded by previous history of hyperthyroidism or hypothyroidism. This is a question with multiple parameters, but we are convinced from clinical evidence that, as long as FT_4 and FT_3 are within normal limits, bone density is being maintained.

Cardiac Risk. Both hyperthyroidism and hypothyroidism are cardiovascular risks.[23] Our patients are quite different. They can only be considered hyperthyroid based on one lab value (TSH) that does not accurately display the patient's condition. Their FT_3, FT_4, and symptomatology indicate normal thyroid function. On the rare occasion that a patient has heart palpitations or other symptoms of overtreatment, we discontinue thyroid treatment temporarily and usually restart at a lower dose.

Furthermore, one must consider the entire system: the famine response is a multi-level adaptation involving down regulation of cellular receptors and intracellular machinery (Table). Thus the available thyroid hormone often does not appear to be as effective as in the non-famine condition. Others concur in finding a lack of hyperthyroid symptoms in their hypocaloric patients on high doses of T_3.[14,24-26]

Nitrogen Depletion. In some studies of thyroid replacement in the hypocaloric state, nitrogen loss was evaluated and found to be excessive. It was concluded that T_3 has catabolic effects on muscles.[13,27,28] However, the hypocaloric diet given in each case provided less protein than required for muscle maintenance under normal conditions. Bray et al.[13,p.719] commented that sufficient dietary protein may eliminate this problem. In one study, adequate protein (74 g/day) was provided. Nitrogen balance reached equilibrium at day 11.[29] In our private practice, our patients are advised to eat adequate protein and we do not see problems with muscle wasting. Several authors provide a more thorough discussion.[13,27,28,30]

7. Broadening the Concept to the Non-dieting Condition

While the most obvious use of these principles is in weight loss patients, our thoughts may apply to general hypothyroid patients as well. Silva's group[31] found that increasing the T_4 dosage while maintaining TSH within normal limits resulted in a significant increase in resting energy expenditure. The authors reported that this difference in daily energy expenditure would be significant for long term weight maintenance. A thorough discussion of this issue is available.[32] The ongoing arguments regarding the acceptable limits of TSH may be the result of vocal patients who realize they feel better when their thyroid dosage is higher. Patients without weight problems also come to us suffering many symptoms of hypothyroidism yet have been told they are euthyroid based on laboratory assessment. If we find low normal FT_3 or FT_4 or high rT_3, we will treat accordingly. Generally, symptoms are resolved with our approach.

Given this wide variety of adaptations preventing weight loss and encouraging regaining of weight, treatment must be explored to help patients. We must recognize obesity as a disease state that requires treatment. While many possible avenues for treatment are being explored, we believe that, for those with symptoms and FT_3, rT_3, and FT_4 levels indicative of the famine state, thyroid treatment is an important and safe approach.

Many patients and clinicians believe weight loss is an achievable long term goal through moderate diet and exercise. With our current knowledge of the highly evolved mechanisms to prevent weight loss discussed here and the intensive amount of work required for successful maintenance of weight loss,[34] it is our job as clinicians to educate our patients that their challenges with weight are not lack of will power but a highly evolved system which can be treated. To continue to view our patients' failures as a weakness of will power is to ignore the reality of this condition and do a major disservice to our patients and society at large.

Conclusion

In our clinical practice, we measure FT_3 and FT_4 and often find them to be at the low end of normal when a patient is suffering from a plateau in weight loss despite strict caloric limitation and exercise. This condition is accompanied by symptoms of low thyroid such as cold, fatigue, depression, constipation, and/or hair loss. rT_3 is often elevated as well. Using individualized approaches to thyroid treatment, we find we generally can eliminate hypothyroid symptoms, but suppression of TSH is the rule, rather than the exception. If a patient maintains a low calorie state and we have treated thyroid abnormalities associated with weight loss, the body will continue to suppress TSH because of the altered feedback set point.

Anecdotally, many patients complain of reaching a plateau when trying to lose weight. This patient observation is in keeping with the concept of an adaptive response to decreased food supply. We now understand that this famine condition is a multilevel neuroendocrine response involving brain centers, circulating hormones, cell membrane transporters, and intracellular receptors and enzymes (Table). But adaptations to a reduced caloric state are not found only in thyroid pathways. Once weight is lost, skeletal muscle becomes more efficient favoring weight gain. For review, see Rosenbaum and Leibel.[12] Neuronal activity in brain areas involved in regulation of eating and hedonic responses are altered after weight loss, making food more desirable.[33]

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Table. Human and rat studies showing objective changes in the hypocaloric or fasting state.

During hypocaloric or fasting state	**Human** Response: **I** = Increase; **D**= Decrease; **NC** = No Change (only statistically significant results in study reported)	**Rat**
TT_3	**D** 800 kcal diet x 10 days; overweight women.[35] **D** 12-week, 1245 kcal diet; obese women.[36] **D** at 1 week, very low calorie diet +/- exercise; obese women.[30] **D** starvation at 1 week; obese men and women.[37] **D** 10 days starvation (returns quickly after refeeding); normal weight men.[38] **D** low calorie (80% energy requirement x 4 weeks, then 50% x 4 weeks); obese/overweight women.[39] **D** 400 kcal 5 days; obese men[40] **D** long term free-living calorie restriction compared with controls; men and women[41] **D** during first 15 days of fasting, then increased until day 30, but not to baseline; after refeeding, increased to baseline by 14 days; obese men and women[42] **D** after 4 days of fasting; obese men and women[43] **D** fasting days 11-20; obese men[44] **D** on day 4, remained low throughout 7-day fast; rose during refeeding; 6 obese women, one each man and woman, non-obese[45] **D** 500 kcal 2 weeks; obese men and women[46] **D** 300 kcal 12 weeks; obese women[47] **D** 4-week fast; obese men and women[48] **D** 60-hr fast; normal weight men and women[49] **D** 6-week reduced calories; obese children[50] **D** 320 kcal up to 13 weeks, by end of week 1, further decreased by week 3 and remained low until re-alimentation; obese men and women[51] **D** during 7 day fast. After 4 days of 200 kcal glucose, increased to peak; obese men and women[52] **D** after 4 weeks starvation; obese men and women[53] **D** 30 hr fast, then **NC** after refed 800 kcal at 1900 hr and sampled for 5 hr; healthy men[54] **D** 1-3 mo after bilio-pancreatic by-pass surgery; men and women[55]	**I** by 14 day of fast; male obese Zucker[56] **D** by 4 days of fast; male lean[56] **D** 72 hr starvation; adult males[57] **D** Fasting: in 1 day; males[58] **D** 15-day food restriction; males[59]

Table. Human and rat studies . . . *Continued*

T3 production	**D** 4-week fast; obese men and women[48]	
FT$_3$	**D** 60 hr fast; hypothyroid men and women[60] **D** after 4 days of fasting; obese men and women[43] **D** fasting days 11-20, decrease %FT$_3$ and absolute FT$_3$ with absolute FT$_3$ returning toward normal during days 24-42; obese men[44] **D** 500 kcal 2 weeks; obese men and women[46] **D** 4-week fast; obese men and women[48] **D** during 7 days of fast, then increased during glucose ingestion; obese men and women[52] **D** 1-3 mo after bilio-pancreatic by-pass surgery; men and women[55] **D** after 4 weeks starvation; obese men and women[53]	
rT$_3$	**I** 800 kcal diet x 10 days; overweight women[35] **I** after 800 kcal diet produced 10% weight loss; obese and normal men and women[61] **I** starvation at 1 week; obese men and women[37] **I** starvation 4 weeks; obese men and women[48] **I** 10 days starvation (returns quickly after refeeding); normal weight men[38] **I** starvation at 1 week; normalized after 4 days refeeding; obese women[17] **I** at 1 week; very low calorie diet +/- exercise; obese women[30] **I** 400 kcal 5 days; obese men[40] **I** significant by day 2 of 400 kcal increasing daily; obese women[62] **I** from detectible in 1/7 pts to detectible in 4/7 pts after 60 hr fast; hypothyroid men and women[60] **I** during first 2 weeks, then return toward normal by day 18; obese men.[44] **I** 30 hr fast, then nonsignificant increase after refed 800 kcal at 1900 hr and sampled for 5 hr; healthy men[54] **I** 500 kcal 2 weeks; obese men and women.[46] **I** 320 kcal up to 13 weeks, rT$_3$ peaked at 1 week remained statistically elevated until week 7; obese men and women[51] **I** during 7 days of fast. Decrease by day 5 of 200 kcal glucose ingestion; obese men and women[52] **I** during first 15 days of fasting, then decreased to approximately baseline at day 30, then stable after refeeding for 14 days; obese men and women.[42] **D** after 4 days of fasting; obese men and women[43]	**NC** Fasting; males[58]

Table. Human and rat studies . . . *Continued*

Free rT_3	**I** during 7 days of fast. During glucose ingestion, decrease; obese men and women[52]	
Plasma clearance rate of rT_3	**D** fasting 7 day; obese women[17]	
T_3:rT_3	**D** 800 kcal diet x 10 days; overweight women[35] **D** at 1 week; very low calorie diet +/- exercise; obese women[30]	
TT_4	**I** after 4 days of fasting; obese men and women[43] **I** 320 kcal up to 13 weeks, increased by 1st week, but returned to baseline by 3rd week and remained there; obese men and women[51] **I** 400 kcal 5 days; obese men[40] **I** after 4 weeks starvation; obese men and women[53] **NC** 12-week, 1245 kcal diet; obese women[36] **NC** very low calorie diet +/- exercise; obese women[30] **NC** 60 hr fast; hypothyroid men and women[60] **NC** longterm free-living calorie restriction compared with controls; men and women[41] **NC** 7-day fast; 6 obese women, one each man and woman, non-obese[45] **NC** in 30 days fasting followed by 20 days re-feeding; obese men and women.[42] **NC** 500 kcal 2 weeks; obese men and women[46] **NC** 4-week fast; obese men and women[48] **NC** 6-week reduced calories; obese children[50] **NC** 60-hr fast; normal weight men and women[49] **D** Fasting days 11-20, with recovery days 24-42; obese men[44] **D** 6 mo calorie restriction; healthy, sedentary men and women[63] **D** 10 days starvation; normal weight men[38] **D** 1-3 mo after bilio-pancreatic by-pass surgery; men and women[55]	**I** by 14 day of fast; male obese[56] **D** by 4 days fast; lean male[56] **D** 72 hr fast; adult males[57] **D** after 1 day fasting; adult male[58] **D** 5 days of food restriction; adult males[59]
T_4 half-life	**I** 300 kcal 12 weeks; obese women[47]	
TT_3/TT_4	**D** 12-14 hr into fast; mildly obese females[64] **D** low cal (80% energy requirement x 4 weeks, then 50% x 4 weeks); obese/overweight women[39]	
TrT_3/TT_4	**I** 48 hr into fast; mildly obese females[64]	

Table. Human and rat studies . . . *Continued*

FT$_4$	**I** 400 kcal 5 days; obese men[40] **I** after 4 days of fasting; obese men and women[43] **I** 500 kcal 2 weeks; obese men and women[46] **I** during fast with nonsignificant change during glucose ingestion; obese men and women[52] **I** 4-week fast; obese men and women[48] **I** 320 kcal up to 13 weeks. I by week 1, then returned to baseline; obese men and women[51] **I** slight after 4 weeks starvation; obese men and women[53] **NC** Fasting days 11-20, no change in absolute FT$_4$ - increase % FT$_4$; obese men[44] **NC** long-term free-living calorie restriction –27% sedentary[41] **NC** 60 hr fast; hypothyroid men and women[60] **NC** low cal (80% energy requirement x 4 weeks, then 50% x 4 weeks); obese/overweight women[39] **D** at 2 weeks on very low calorie diet; obese men and women[37]	**NC** by 14 day of fast; obese males[56] **D** by day 4 of fast; lean males[56]
TSH	**D** very low cal diet or fasting at 2 weeks; obese men and women[37] **D** slight. 10 days starvation; normal weight men[38] **D** to < 1 mU/L; after 30 hr fast. After refed 800 kcal at 1900 hr and sampled for 5 hr, nonsignificant increase; healthy men[54] **D** low calorie (80% energy requirement x 4 weeks, then 50% x 4 weeks); obese/overweight women[39] **D** during days 1&2 fast combined versus 2 days pre-fast, with gradual increase starting on day 3; 6 obese women, one each man and woman, non-obese[45] **D** after 4 days of fasting; obese men and women[43] **NC** after 60 hr fast; hypothyroid men and women[60] **NC** 400 kcal 5 days; obese men[40] **NC** at 2 weeks +/- exercise; obese women[30] **NC** 60-hr fast, TSH did not change (however, 60 hrs = 2.5 days so exact opposite time in day for reading and TSH has a diurnal rhythm, so numbers are not comparable); normal weight men and women[49] **NC** Fasting days 11-20; obese men[44] **NC** 6-week reduced calories; obese children[50] **NC** 320 kcal up to 13 weeks; obese men and women[51] **NC** 4 weeks starvation; obese men and women[53] **NC** 1-3 months after bilio-pancreatic by-pass surgery; men and women[55]	**D** 72 hr starvation; adult males[57] **D** 15 days of food restriction; adult male[59] **D** fasting in 1 day; males[58]

Table. Human and rat studies . . . *Continued*

TSH diurnal rhythm	Eliminated within 24 hr of onset of fasting; 6 obese women, one each man and woman, non-obese[45] Eliminated after 30 hr fast; healthy men[54]	
Resting metabolic rate	**D** 800 kcal diet x 10 days; overweight women[35] **D** 6-week reduced calories; obese children[50]	
Basal metabolic rate	**D** 300 kcal 12 weeks; obese women[47]	
Core body temperature	**D** calorie restriction x 6 mo; +/-exercise for 24h temperature; healthy, sedentary men and women[63] **D** calorie restriction x 6 mo; +exercise for night temperature; healthy, sedentary men and women[63] **NC** very low calorie diet; healthy, sedentary men and women[63]	
24-hr energy expenditure	**D** calorie restriction x 6 mo. +/-exercise or very low calorie diet; men and women[63] **D** 48-hr fast; lean and obese Pima Indian and Caucasian men[65]	
Sleeping metabolic rate	**D** 48-hr fast; lean and obese Pima Indian and Caucasian men[65]	
24-hr respiratory quotient	**D** 48-hr fast; lean and obese Pima Indian and Caucasian men[65]	
Mononuclear leukocyte nuclear T_3 binding sites	**NC** (80% energy requirement x 4 weeks, then 50% x 4 weeks); obese/overweight women[63]	
TSH response to TRH stimulation	**NC** after fasting at 2 weeks, then increased after 30 days of realimentation; obese men and women.[42] **NC** after 4 weeks starvation; obese men and women[53] **NC** 300 kcal 12 weeks; obese women[47] **D** peak and integrated response after 60 hr fast; hypothyroid men and women[60] **D** Peak after 4 days of fasting; obese men and women[43] **D** 7-day fast; obese men and women[52] **D** after 3-9 weeks of fasting; obese men[44]	
TT_3 response to TRH stimulation	**NC** in delta TT_3 after 4 days of fasting; obese men and women[43] **NC** after 4 weeks starvation; obese men and women[53] **NC** after 7-day fast: i.e., no change in delta of response but starting from lower baseline; obese men and women[52]	

Table. Human and rat studies . . . *Continued*

T_4/TBG	**I** during 30 days fasting, then remained elevated during re-feeding; obese men and women.[42]	
T_3/TBG	**D** during first 15 days of fasting then increased during next 15 days, and continued to increase during re-feeding; obese men and women[42]	
Free T_3 index	**D** 320 kcal up to 13 weeks, decreased by week 1 and remained low until refeeding; obese men and women[51]	
FT_4I	**I** 320 kcal up to 13 weeks, increased by week 1, then returned to baseline; obese men and women[51]	
Serum TBG	**NC** 320 kcal up to 13 weeks; obese men and women[51]	
Thyronine-binding globulin	Inconsistent at 2 weeks +/- exercise; obese women[30] **D** 500 kcal 2 weeks; obese men and women[46]	**I** by 14 day of fast; obese males[56] **I** by 14 day of fast; lean males[56]
T_4 binding prealbumin	**D** 500 kcal 2 weeks; obese men and women[46]	
Albumin	**NC** 500 kcal 2 weeks; obese men and women[46]	
T_3 Metabolic Clearance Rate	**NC** 4-week fast; obese men and women[48]	
T_4 Metabolic Clearance Rate	**NC** 4-week fast; obese men and women[48]	
T_4 production rate	**NC** 4-week fast; obese men and women[48]	
Hepatic T_4 to T_3 conversion		**D** 2-day starvation; adult males[67] **D** 2-day starvation, then add carbohydrates: **I**; adult males[67] **D** 2-day starvation, then add amino acids: **I**; adult males[67] **D** 2-day starvation, then add lipids: **NC**; adult males[67]
Tubular reabsorption of T_4 and T_3	**D** 3-day fast; healthy adult men and women[16]	

Table. Human and rat studies . . . *Continued*

Hepatic T_3 production		**D** fasting; males[58]
Hepatic rT_3 degradation		**D** fasting; males[58]
Hepatic uptake of T_4 by cell membrane transporters	**D** 600 kcal diet for 10-14 days; euthyroid obese subjects (gender not stated)[68]	**D** fasting x day 3; **NC** if provide liver with T_4[69]
Pituitary nuclear T_3 content		**D** fasting 72 hr; adult males[57]
Pituitary nuclear receptor		**D** fasting 72 hr; (results in equal or greater receptor occupancy than controls); adult males[57]

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Thyroid Science 5(7):1-6, 2010

Effect of Exogenous Thyroid Hormone Intake on the Interpretation of Serum TSH Test Results

(Full Text Free in pdf format)

Peter Warmingham, BSc (Hons), MIET

Derby UK (Biography)
Correspondence: peter@warmingham.plus.com

Introduction

Dr. John C. Lowe, Editor-in-Chief

Many examples in the history of science show that landmark advances in particular scientific fields often come from specialists in other fields. I firmly believe this is the case with Peter Warmingham and his hypothesis about the conventional error of using the TSH to adjust patients' dosages of thyroid hormone during their treatment for hypothyroidism.

As a way to introduce Peter Warmingham, I will briefly mention one of the many examples of landmark changes in scientific fields brought about by the thinking of specialists in other fields. Alfred Wegener is now recognized as the founding father of one of the major scientific revolutions of the 20th century, the concept of continental drift and plate tectonics. His hypothesis of continental drift came to him in 1912 and he announced the hypothesis in 1915. In the hypothesis, Wegener argued that all continents were once joined together in a single landmass and have drifted apart.

His book on the theory was published in the US in 1925. Its appearance set off vehement opposition by prominent geological scientists. Some of them disdainfully dismissed Wegener's hypothesis using the logical fallacy called *ad hominem*; that is, rather than debating the evidence he presented, they argued that he was wrong because he was not a geologist. This was true: Wegener was an astronomer who specialized in meteorology and climatology.

I mention Wegener and the logical fallacy used to denounce his hypothesis because I anticipate the same fate for Mr. Warmingham's hypothesis. The endocrinology specialty often uses the logical fallacy when researchers or clinicians not board certified in endocrinology present evidence that conventional beliefs of the endocrinology specialty are false. For example, when Dr. Steven Hotze challenged Dr. Bill Law (at the time President of the American Association of Clinical Endocrinologists) to debate on national television desiccated thyroid vs levothyroxine, Dr. Law declined. Among his reasons was that *only* board certified endocrinologists, which Dr. Hotze was not, are qualified to publicly comment on the treatment of hypothyroidism. If *ad hominem* is used to denounce the "Warmingham TSH Hypothesis," as I call it, I want our subscribers to recognize the fallacy and to appreciate its total irrelevance to whether or not the Warmingham hypothesis is right or wrong.

Intense opposition to Wegener's theory continued into the 1950s. But by the 1960s, accumulated scientific evidence showed that Wegener had been right. At the same time, it showed that prominent geological scientists who had scorned his theory were wrong. Modern plate tectonics is the direct descendent of Wegener's theory of continental drift. Today, plate tectonics is a thriving and productive scientific field. And humanity benefits from this field for a reason important to note: largely *because Wegener's knowledge of scientific fields other than geology* gave him a parallactic view of the origin of continents—a view that *correctly* meant that the contrary views of geologists had to be wrong. His parallatic view—rebuked by many because he was not a geologist—seeded the scientific soil for the fruitful growth of the science of geology from the 1960s on.

Examples such as Wegener's lead me to value proferted intellectual insights from those in fields other than thyroidology who nevertheless are knowledgeable in various aspects of thyroidology. Peter Warmingham is an exemplary example. He is an electrical and electronics engineer with special knowledge of control systems. The pituitary-thyroid axis is a biological control system, one which Mr. Warmingham clearly understands. His landmark hypothesis shows how a facility essential for successful performance in engineering—that is, exacting precision in analytical thought—has enabled him to see clearly what so many thyroidologists have long failed to see.

Mr. Warmingham's hypothesis is straightforward: When a hypothyroid patient (whose circulating pool of thyroid hormone is too low) begins taking exogenous thyroid hormone, a negative feedback system reduces the pituitary gland's output of TSH. This decreases the thyroid gland's output of endogenous thyroid hormone, and despite the patient's exogenous thyroid hormone's contribution to his or her total circulating thyroid pool, that pool does not increase—not until the TSH is suppressed and the thyroid gland is contributing no more thyroid hormone to the total circulating pool. At that point, adding more exogenous thyroid hormone will finally increase the circulating pool of thyroid hormone. The increase must occur for thyroid hormone therapy to be effective. The patient's suppressed TSH, then, does not indicate that the patient is over-treated with thyroid hormone; instead, it indicates that the patient's low total thyroid hormone pool will finally rise to potentially adequate levels.

The implication of the Warmingham TSH Hypothesis is clear: In general, if the clinician denies the patient more exogenous thyroid hormone because his or her TSH level is suppressed, the clinician will deny the patient enough thyroid hormone to increase the circulating pool of the hormone to a level adequate for maintaining normal thyroid hormone-driven cellular metabolic processes. But if the clinician continues to increase the patient's thyroid hormone dosage based on relevant measures of physiological function, such as the basal temperature, then the patient's health will be properly served *despite his or her suppressed TSH level*.

With this introduction, *Thyroid Science* presents to our subscribers what we believe to be a hypothesis of *supreme* importance to the proper treatment and health and well-being of hypothyroid patients.

Warmingham, P.: Effect of exogenous thyroid hormone intake on the interpretation of serum TSH test results. *Thyroid Science*, 5(7)1-6, 2010.

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Thyroid Science 5(7):1-6, 2010

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Hypotheses

Effect of Exogenous Thyroid Hormone Intake on the Interpretation of Serum TSH Test Results

Peter Warmingham, BSc (Hons), MIET
Derby UK (See Bio)
Correspondence: peter@warmingham.plus.com

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Introduction

The dosage of thyroid hormone for hypothyroid patients is usually set such that the TSH reading is within the reference range. At this dosage the physician regards the patient as being "balanced," yet the patient often complains that this dosage is not sufficient to restore his or her feeling of well being.[1,11] This method of determining the optimum dosage of thyroid hormone is based on the assumption that the TSH results can always be interpreted in the same way regardless of whether or not the patient is on thyroid hormone medication. This paper will use a control systems approach to hypothesise that this assumption is incorrect.

The hypothesis presented in this paper is supported by the data presented in the McKenna et al. study.[12]

The Thyroid System

A block diagram of the thyroid system is presented in Figure 1. The thyroid gland produces T_3 and T_4 under the controlling influence of thyroid stimulating hormone (TSH) secreted by the pituitary gland. The T_3 and T_4 produced by the thyroid gland are released into the blood stream for distribution to all metabolically active cells. The levels of T_3 and T_4 in the blood stream are sensed by the thyrotrophs of the anterior pituitary gland and compared with the desired levels predetermined by hypothalamic thyrotrophin releasing hormone (TRH). In effect, the TRH provides a set point about which to regulate the serum T_3 and T_4 levels.[4,5]

If the serum T_3 and T_4 levels fall, the pituitary gland secretes more TSH which stimulates the thyroid gland to produce more T_3 and T_4. Conversely, if the serum T_3 and T_4 levels rise, the pituitary gland secretes less TSH, so causing the thyroid gland to produce less T_3 and T_4. Hence, there exists a negative feedback loop, the purpose of which is to regulate serum T_3 and T_4 at the desired level as the demand for T_3 and T_4 varies.

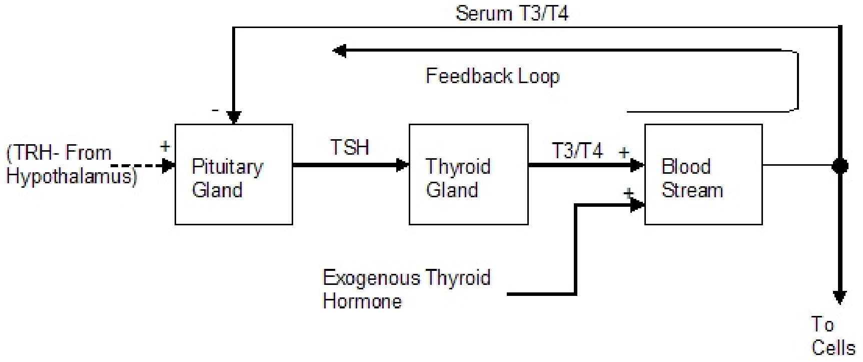

Figure 1. Block diagram of the thyroid system.

Exogenous thyroid hormone passes directly into the blood stream, adding to thyroid hormone produced endogenously. The combined exogenous and endogenous hormone begin to raise the serum T_3 and T_4 levels. However, the negative feedback loop quickly acts to compensate for the increased thyroid hormone level by reducing TSH, hence reducing the output of T_3 and T_4 from the thyroid gland. As the exogenous dose of T_3/T_4 increases, so the proportion of endogenously produced T_3/T_4 in the blood serum decreases.

Depending on the combined "gain" in the pituitary gland and/or the thyroid gland, the decrease in the endogenous production of T_3/T_4 may be less than, equal to, or greater than the increase in exogenous thyroid hormone intake. This variation in the ratio of endogenous to exogenous thyroid hormone results in under, exact or over-compensation respectively as described in this paper.

As the exogenous dosage increases, the feedback action results in a significant reduction in TSH. The reduced TSH is accompanied by a relatively insignificant change in the serum T_3 and T_4 levels up to the point where TSH suppression occurs. At that point, the T_3 and T_4 output of the thyroid gland can no longer be significantly reduced.

In Figures 1 through 6, the conversion of T_4 into T_3, which takes place in several tissues but mainly the liver, kidneys and thyroid gland,[6] has been ignored in order to simplify the model.

TSH Levels

A patient who is not on thyroid hormone replacement therapy, and whose thyroid gland is producing too much T_3/T_4, is said to be hyperthyroid. As this condition develops, negative feedback action compensates by reducing TSH. At the point where TSH suppression first occurs, the serum T_3/T_4 levels are almost unchanged, as shown in Figure 2.

As the condition progresses further, the serum T_3 and T_4 levels rise. By the time the patient has developed symptoms of hyperthyroidism and presented them to his or her physician, it is not unreasonable to assume that a diagnosis based on the suppressed TSH level can confidently be made (provided that the pituitary gland is working normally). It is considered by some authorities that if severe enough and left untreated, this situation will lead to cardiac problems and reduced bone mineral density.

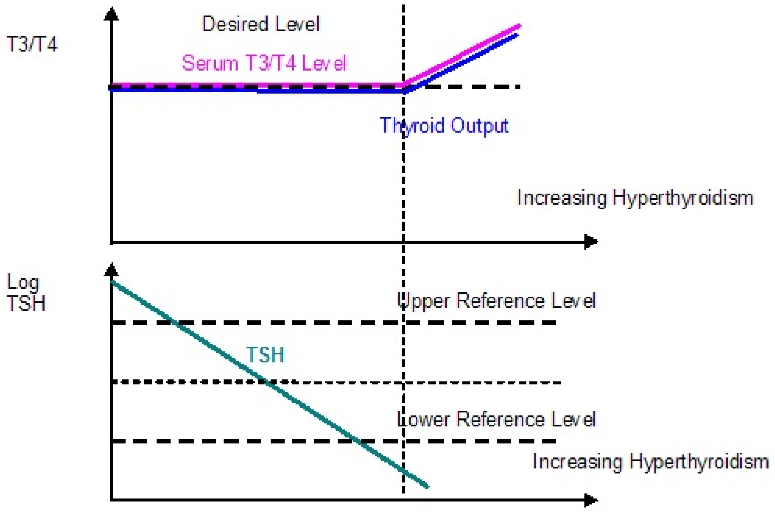

Figure 2. Serum T3/T4 and TSH levels in progressing hyperthyroidism.

However, when a hypothyroid patient is started on a low dose of thyroid hormones, the feedback loop begins to compensate for the exogenous supply of T_3/T_4. The feedback loop compensates by reducing TSH and hence endogenous T_3/T_4 production, as shown in Figure 3. As the exogenous dose increases further, TSH decreases, but the serum T_3/T_4 levels do not start to increase until TSH suppression occurs. A suppressed TSH does not necessarily mean, therefore, that the patient has become hyperthyroid with the attendant risks mentioned above.

The physician, of course, will want to avoid over-treating the patient. To avoid over-treatment, the physician is unlikely to prescribe a dose of thyroid hormone higher than that which has suppressed the patient's TSH. The physician, then, uses the suppressed TSH level as his or her primary gauge of the adequacy of treatment. However, the hypothesis presented in this paper proposes that a suppressed TSH in a patient undergoing thyroid hor-

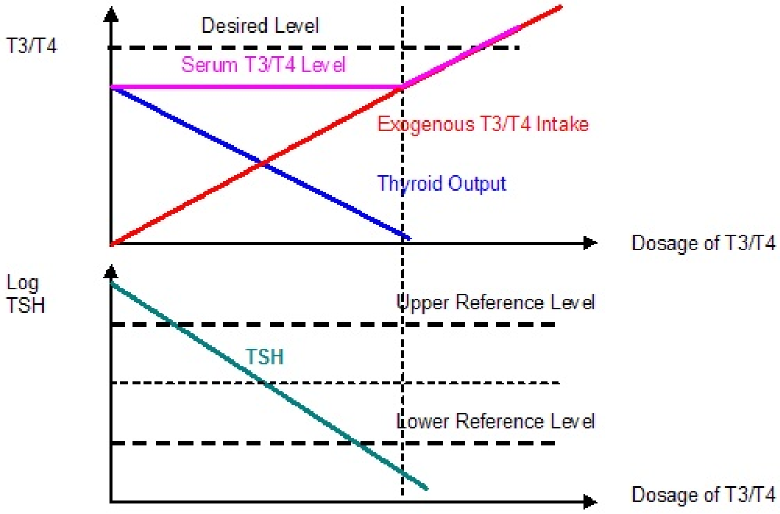

Figure 3. Serum T3/T4 and TSH levels with increasing exogenous dose.

mone treatment should not be the primary determinant of the adequacy of treatment. The hypothesis further proposes that the patient's pituitary/thyroid feedback loop has effectively lowered endogenous thyroid hormone production and suppressed the TSH as the appropriate physiological adjustment to the patient's exogenous thyroid hormone. However, the suppressed TSH does not accurately gauge whether the patient's exogenous thyroid hormone dosage is insufficient, excessive, or adequate. This determination can be made only through consideration of the tissue effects of exogenous thyroid hormone.

If the proposed hypothesis is correct, then the patient's TSH level has ceased to be a useful test of the adequacy of thyroid hormone intake. Instead, the proper action for the physician is to look to test results that indicate tissue effects of thyroid hormone to decide whether the patient's thyroid hormone intake is too low, too high, or adequate. Such tests include the basal temperature and/or pulse rate, serum T_3/T_4 level, and symptoms.

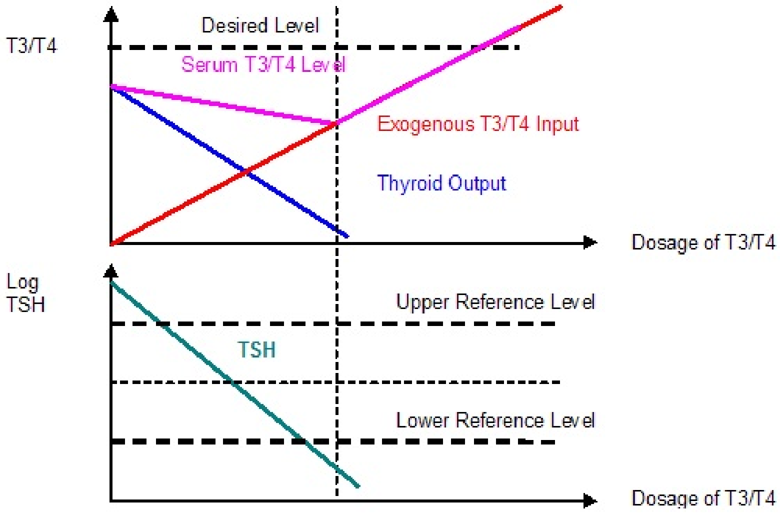

Figure 4. Serum T3/T4 and TSH levels with increasing exogenous dose (feedback loop over-compensating).

Exact Compensation. Figure 3 illustrates exact compensation whereby the increase in exogenous T_3/T_4 intake is exactly matched by a decrease in thyroid gland output up to the point where TSH suppression occurs. Because of the action of the feedback loop, therefore, a suppressed TSH when the patient is on medication cannot necessarily be interpreted as meaning that the patient is hyperthyroid—not unless the exogenous dosage really is excessively high. Indeed, it is quite likely that the serum T_3/T_4 levels have not increased at all.

Over Compensation. Figure 4 illustrates over-compensation whereby the reduction in endogenous T_3/T_4 production exceeds the increase in the exogenous dose. It can be seen that the serum T_3/T_4 levels reduce up to the point where TSH suppression occurs. It is also evident that the serum T_3/T_4 levels show no increase over their pre-treatment levels until the exogenous dose exceeds that required to just cause TSH suppression.

Again, a suppressed TSH does not necessarily mean that the patient is hyperthyroid. Furthermore, an exogenous dose that does not exceed that which just causes TSH suppression may actually result in an unintended reduction in serum T_3/T_4 levels, as manifested by an unexpected increase in the severity of the patient's symptoms.

Under Compensation. Under-compensation, whereby the reduction in endogenous T_3/T_4 production is exceeded by the increase in exogenous T_3/T_4 dose, is illustrated in Figure 5. It can be seen that although there is some increase in the serum T_3 and T_4 levels relative to the pre-treatment levels, up to TSH suppression, the full benefit of treatment is not gained until the exogenous dosage exceeds that required for TSH suppression.

Again, a suppressed TSH does not necessarily mean that the patient is hyperthyroid. Furthermore, whilst there may be a modest reduction in the severity of the patient's symptoms up to TSH suppression, this reduction may well be less than the physician hoped for.

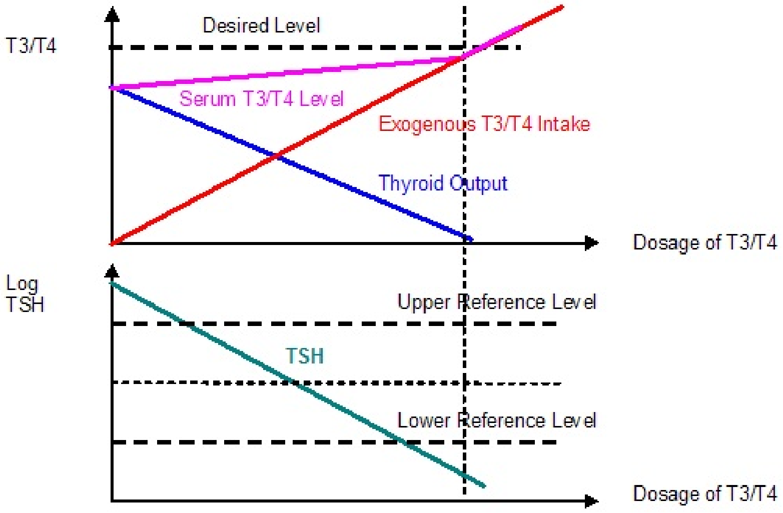

Figure 5. Serum T3/T4 and TSH levels with increasing exogenous dose (feedback loop under-compensating).

Relationship Between TSH and T_4. In the preceding analysis it has been assumed, for clarity, that there is an inverse logarithmic relationship between T_4 and TSH. However, Professor Rudolf Hoermann et al. have shown that a much more dynamic and non-linear relationship exists between T_4 and TSH.[2]

Some authorities have spoken of "the exquisite sensitivity of TSH." The new model proposed by Professor Rudolf Hoermann et al.,[2] however, shows that "the response of pituitary TSH depends on the deviation of circulating free T_4 from an optimum set point and may turn out less vigorous and exaggerated as the magnitude of the deviation decreases." Figure 3 must therefore be modified as shown in Figure 6 (a piecewise linear presentation of the T_4/TSH relationship has been used for clarity).

It can be seen from Figure 6 that there is effectively a "dead-band" in the region of the set point where the feedback action will be weaker. In electronic control systems, a dead-band may be deliberately introduced to prevent instability. It is suggested that the dead-band in the thyroid feedback loop may have a similar function. Nevertheless, the pituitary-thyroid-pituitary feedback loop will still compensate for the exogenous dose by reducing the output of the thyroid, whatever the actual form of the T_4/TSH relationship. However, physicians who set the dosage of thyroid hormone at a level which reduces TSH to about mid range will be working, albeit unwittingly, at the portion of the TSH/T_4 relationship where the pituitary TSH response is weakest. This will compound the errors and uncertainties involved when using TSH levels to set the thyroid hormone dose.

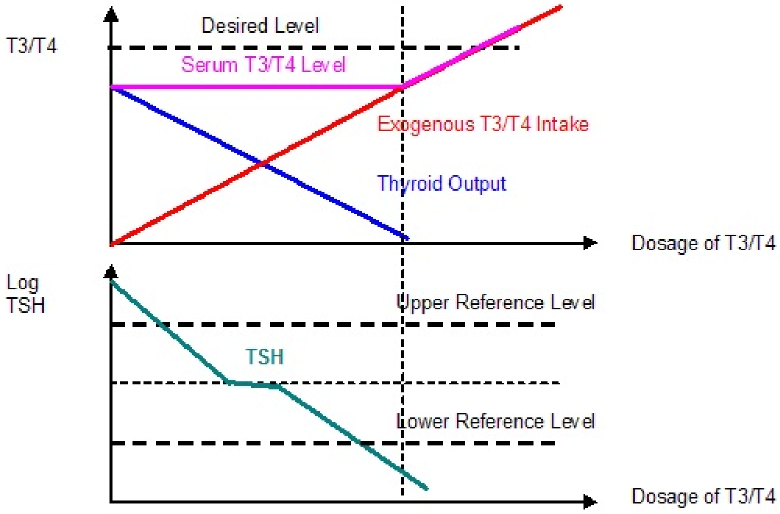

Figure 6. Serum T3/T4 and TSH levels with increasing exogenous dose (non-linear T4/TSH relationship).

Discussion

In diabetes, the correct dose of insulin required can be determined by regularly checking the blood glucose levels. The blood glucose measurement is a direct check on the downstream effect of insulin and no inferential measurements are involved.

In hypothyroidism, on the other hand, the only measurements that are equivalent to the glucose in the insulin example, as downstream effects of thyroid hormone on the metabolic processes in the cells, are basal temperature[7] and metabolic rate measurements.[3,8,9,10] However, it is more usual for physicians treating hypothyroidism to infer that the thyroid hormone level in cells is normal from an upstream measurement—serum T_3/T_4 levels. This is not a reliable inference to make because numerous mechanisms of thyroid hormone resistance can substantially alter the relationship between the serum and cell T_3/T_4 levels, as Tjorve et al.[3] have described.

When the serum T_3/T_4 levels are then inferred from a measurement of TSH instead of being measured directly, two levels of inference have taken place, the results of which should be treated with a high index of suspicion.

Conclusions

1. The TSH reading alone is valid only when the patient is not on thyroid hormone replacement therapy, but even then there are two levels of inference between it and the thyroid hormone levels in cells other than the pituitary thyrotrophs. Within the double inference there will be many interpretation errors.
2. The sensitivity of the TSH reading varies relative to the set point, and is least sensitive in the region of the set point.
3. Hypothyroid patients whose thyroid hormone replacement dose is being regulated against the TSH reading alone are being maintained in an under-treated state and are correct to assert that they feel better on a higher dose. Therefore, hypothyroid patients should not have their thyroid hormone dosages set by reference to their TSH readings.
4. Clinical studies should be carried out to confirm the hypothesis presented in this paper.

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Thyroid Science
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Thyroid Science 3(2)H1-14, 2008

Hypothyroidism: Sensitive Diagnosis and Optimal Treatment of All Types and Grades—A Comprehensive Hypothesis

Based on a Review of the Standard and "Alternative" Literature and Extensive Clinical Experience

(Full Text Free in pdf format)

John V. Dommisse, MD, MBChB, FRCP(C)*

*Nutritional & Metabolic (Tele)Medicine, 1840 E. River Road, Suite 210, Tucson, AZ, 85718-5892
Contact: www.JohnDommisseMD.com John@JohnDommisseMD.com

Abstract. The hypothesis of this paper is that hypothyroidism (in its various forms and degrees) is often undiagnosed in its grade 3 primary, secondary (pituitary), tertiary (hypothalamic), and non-thyroidal illness hypothyroidism versions; and under-treated in all versions, including its grades 1 and 2 primary hypothyroidism versions. The current standard and alternative approaches to the diagnosis and management of hypothyroidism, and their logical inconsistencies and inadequacies, are discussed. The biggest losers in this neglectful situation are elderly, memory- loss, mood-disordered, chronically fatigued, or overweight patients.

An extensive review is presented, which is then coupled with logical argument and clinical experience to clarify the hypothesis. Methods employing the free thyroid hormone levels (FT4 and FT3), by the accurate direct- and tracer-dialysis methods, respectively, and a lower normal range for the thyroid stimulating hormone level are described. These help optimize the newly-developed diagnostic strategies. Their superiority over the standard conventional and alternative approaches are suggested by inferential argument and by the author's personal experience of his own case of post-surgical (thyroglossal cystectomy) hypothyroidism—missed by the medical profession for 36 years—and his clinical experience with approximately 5,000 patients over a 19-year time period.

Diagnostic strategies and treatment methods are described which refute traditional objections to measuring the FT3 serum level—at least in the case of the serum test done by the dialysis method—and to treating with varying combinations of both T4 and either T3 or T4/T3 combination hormone preparations. The objections about aggressive thyroid treatment causing or aggravating osteoporosis and cardiac arrhythmias are found (in the author's practice) to not only be overblown, but to be entirely non-existent when corrections are made for certain mineral, vitamin, amino acid, and sex- and growth-hormonal deficiencies.

Keywords: Absence of osteoporotic and cardiac-arrhythmic effects • Dialysis free T3 measurement and optimal correction • Hypothyroidism • Optimal 24-hour T3 serum level correction • Types and grades

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Thyroid Science 3(2):H1-14, 2008 www.ThyroidScience.com *Hypotheses*

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John V. Dommisse, MD, MBChB, FRCP(C)*

*Nutritional & Metabolic (Tele)Medicine, 1840 E. River Road, Suite 210, Tucson, AZ, 85718-5892
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Keywords: Absence of osteoporotic and cardiac-arrhythmic effects • Dialysis free T_3 measurement and optimal correction • Hypothyroidism • Optimal 24-hour T_3 serum level correction • Types and grades

Background

While overt hypothyroidism is easily diagnosed by physicians, the primary illness can be less apparent in its early or so-called "subclinical" stages.[4][54] Central, secondary and tertiary,[49] and non-thyroidal illness/"euthyroid-sick" syndrome[13][19][47] hypothyroidism are also overlooked by the current conventional diagnostic approach which frequently relies exclusively on the ultra-sensitive serum thyroid stimulating hormone (TSH) level. It is important to recognize that the ultra-sensitive TSH is an *indirect* test with a "normal range" that is useful for diagnosing *grades 1, 2, and 3 primary* hypothyroidism *only* (see next section, "The Grades of Primary Hypothyroidism"). In the United States, a free T_4 (FT_4) level is sometimes obtained and occasionally a total or free T_3 (FT_3) level, but a free T_3 level by the tracer-dialysis method, the only accurate indicator of this exclusively-active hormone's function, is rarely obtained. This is astounding, considering that T_3 is the "final common pathway" of the metabolism of thyroid hormones and is the main active version of the hormone.

The Grades of Primary Hypothyroidism

A patient is considered to have grade1 primary hypothyroidism when his or her serum FT_4 level (and possibly the total T_3 and/or FT_3 level) is below the normal range, and the ultra-sensitive TSH is way above its normal range.[18][25][32][33][73] Grade 2 primary hypothyroidism is diagnosed when the FT_4 and FT_3 levels are in the lower half of their normal ranges but the sensitive TSH is elevated above its "normal range" of approximately 0.4-2.5 mIU/L.[81] Many physicians have also come to recognize a grade 3 hypothyroidism: FT_4, FT_3, and sensitive TSH all in their normal ranges but the TRH-stimulated TSH jumps up >20 points within 30 minutes. Since the advent of the ultra-sensitive TSH, it has been realized that the TRH-stimulation test of the TSH is not necessary.[46] It became apparent that a positive TRH-stimulated TSH test always results from an ultra-sensitive basal TSH in the higher part of its "normal range," and thus such a high-normal ultrasensitive TSH level on its own signifies grade 3 hypothyroidism.[54]

Only about 5% of the physicians in the U.S. treat grade 3 hypothyroidism, and the author is proud to count himself among them because he has never had a case that did not respond positively, in numerous ways, to his correction of that state. The current conventional approach appears to be tailor-made for many unpleasant surprises; just as one example, covert/"subclinical"/grade 3 hypothyroidism can present initially as a myocardial infarction.[42]

Patients with "subclinical" hypothyroidism, who have the qualifying proposed serum thyroid hormone profile discussed above, almost always have multiple classic symptoms and signs of hypothyroidism. As one authorship has stated, "The presence or absence of symptoms, in both hypothyroidism and 'subclinical' hypothyroidism, depends more on the clinician than on the patient."[29]

In other words, even "subclinical" hypothyroid patients have symptoms (making the term a misnomer); it is just that the physician frequently does not elicit the symptoms and signs. This view is backed by the papers of Staub et al, and Zulewski et al, respectively, which clearly showed significant changes in a clinical symptom index (the Billewicz scale) in "subclinically" hypothyroid women of mean age 50, compared to age-matched controls;[62] and showed significant correlation with serum free thyroxine and TSH levels.[80]

Some physicians regard hypothyroidism as far more common than is generally acknowledged. This article will detail how patients who *are* being treated are actually under-treated because of excessive reliance on the ultra-sensitive serum TSH level for monitoring, and the use of a single thyroid hormone, thyroxine (T_4), in its treatment. Additionally, there are excessive fears of precipitating or aggravating osteoporosis. Evidence for these fears is equivocal and shared by concerns that both natural and iatrogenic hypo- *and* hyperthyroidism may cause the condition.[1][8][30][34][55][71] Apparently, under-treatment of either thyroid state is a risk factor as well.

The conservative American College of Physicians has found enough evidence of the widespread nature of hypothyroidism to recommend that women over 50 years of age be screened for it once every 5 years[36] (since women are 9 times more likely than men to become hypothyroid). In an editorial rebuttal, renowned thyroidologist David Cooper argues for a more aggressive approach to case-finding: 5-yearly screening of women beginning at age 35 and treatment of milder degrees of hypothyroidism.[17] He cites powerful support[3][65] including that of the American Thyroid Association.[60]

A recent estimate of the widespread prevalence of primary hypothyroidism suggests a figure of 9-10% in the United States. This estimate was limited to *active, uncorrected* grades 1 and 2 primary hypothyroidism, and was based on a survey of serum TSH levels on >26,000 adults at a health fair.[53] Only about 10% of those thus identified as hypothyroid admitted to being diagnosed and treated (by definition, inadequately!) despite the long-term health risks associated with the condition. Results of the study were first presented at the October 1997 annual meeting of the American Thyroid Association held in Colorado Springs. These researchers also discovered a strong relationship between an underactive thyroid and elevated serum cholesterol levels, as other investigators also have.[20][29][34][45] T_3 is more effective than T_4 in lowering excess lipid levels and in decreasing the risk of coronary and cerebral arterial occlusion in even subtly-hypothyroid patients.[23]

"Euthyroid-Sick"/Non-Thyroidal Illness/T_3-Hypothyroidism

Another condition that is increasingly being regarded as not necessarily always free of thyroidal functional effects or of the potential benefits of treatment is the "euthyroid-sick/non-thyroidal illness/low-T_3 syndrome."[13][19][47] In this condition the FT_3 level (and sometimes the total T_3 level, the FT_4 level, or the Free Thyroxine Index—FTI or T_7) is below normal and the TSH is normal or even low-normal.[46] This is not due to pituitary or hypothalamic problems but instead to other extrathyroidal illness. It is important not to over-treat this condition when it is present in acute cardio-arrhythmic or other severe potentially life-threatening illness because in these cases the low FT_3 (or FT_4 or FTI) may be potentially life-saving by lowering the metabolic and/or cardiac rate. However, the majority of so-called "euthyroid sick" cases these days appear to occur in chronic ambulatory conditions such as chronic fatigue syndrome, "dysmetabolic syndrome X," or depression. In these conditions, the low FT_3 function not only is *not* helpful but is actually harmful, and is helping to perpetuate the fatigued[13][19][47] or depressed state.[15][38][76]

The validity of the "euthyroid sick" syndrome was first questioned in the 1980s. It had become common for psychiatrists to find that in refractorily depressed patients who had been passed as euthyroid by endocrinologists, serum T_3 levels were low[38] and T_3 administration, more so than T_4, actually "enhanced the effectiveness of the antidepressants."[15][31][39][66][76] In 1990, Palazzo and Suter[47] also published their earlier questioning of the so-called "euthyroidism" of the "sick euthyroid" patients they were seeing in an intensive care unit in England.

Psychiatrists have known for a long time that even in the absence of diagnosed hypothyroidism low T_3 levels are actually causative factors in depression.[38] The depression is rendered refractory by the low T_3 state, and will frequently not respond to any antidepressant medication unless T_3 is used to "augment" the antidepressant medication.[15][31][39][66] In bipolar-affective-disordered/manic-depressive patients, leading psychiatrists have advocated and successfully used thyroid hormone treatment, especially supraphysiologic doses of T_4, to help reduce the frequency and severity of the moodswings.[26][61][74] In approximately one-sixth of individuals on lithium therapy, thyroid function is lowered to a frankly hypothyroid level.[6] When a more inclusive definition of hypothyroidism is used, there may be substantial numbers of other patients who should be considered to be rendered hypothyroid by lithium. So, many of the psychiatric cases who are regarded as euthyroid may in fact be cases of grade 3 primary hypothyroidism, secondary or tertiary hypothyroidism, or "euthyroid sick syndrome" hypothyroidism. The term "euthyroid sick" is now being openly disputed,[13][19][47] meaning that the T_3 used in *augmenting antidepressant treatment* may in fact be a "back-door" entry to the *thyroid* treatment of refractorily depressed hypothyroid patients,[15] until now regarded as euthyroid by the current approach to diagnosis.

The Current Standard and "Alternative" Approaches

Three popular reference texts on the thyroid[9][10][16] point to the great functional importance of T_3 thyroid hormone. It is 9 times more physiologically active in comparison to the T_4 hormone. The T_4 hormone merely serves as a pro-hormone or pre-hormone, with the possible exception of the brain's apparent need for a significant amount of T_4 for optimal function. T_4 is transported more briskly through the choroid plexus/"blood-brain barrier" than is T_3. Thus, brain cells rely heavily on conversion of T_4 to T_3 for their functional supply of thyroid hormone.[75][76]

Despite this broad agreement on the roles of the two thyroid hormones, when it comes to hypothyroidism diagnosis, these texts often advocate only the ultra-sensitive serum TSH level and sometimes a FT_4 *or* a Free Thyroxine Index (FTI or T_7), but no FT_3 level. These experts recommend the sole use of T_4 for treatment in nearly all cases. This paper will present evidence for the inclusion of the FT_3 and FT_4 levels in all thyroid screening and monitoring. It will also support the strategy of including T_3 thyroid hormone together with T_4 in the treatment of most cases of primary, and all cases of secondary, tertiary, *and* non-thyroidal illness hypothyroidism. This is implied by Escobar-Morreale et al with their discovery of the inadequate reversal of post-ablative hypothyroidism in rats by T_4-only treatment.[24] *If the TSH, FT_4, and FT_3 levels serve any diagnostic function at all, they do so only as an integral group of tests, each of which is in a reciprocal relationship to the others.* The Escobar-Morreale study demonstrated that adding T_3 to the replacement regimen did restore euthyroidism to rat tissues.

The major theoretical and practical reasons for the T_4-only treatment approach in the past centered around the greater *stability* of the T_4 blood level in comparison to the T_3 level, which has wider diurnal and post-dose fluctuations.[12] The inaccuracy of the older tests for the T_3 hormone also contributed to this perspective. However, the diurnal variation of T_3 in the untreated human is fairly low; twice- to thrice-daily dosage of all treatment preparations containing

T_3 eliminates this objection in treated cases. Additionally, newer technology has provided the ready availability of the very accurate FT_3 and FT_4 blood levels by the dialysis methods.[63] These factors have erased the validity of the current conventional approach. They have also removed the validity of the non-specific basal-temperature-recording "alternative" diagnostic and monitoring method of Broda Barnes as described in his 1976 book,[5] even if that method was very valuable at the time when accurate T_3 testing was not available.

The traditional, cheap, older tests of thyroid function, the serum total T_4, T_3-uptake, FTI, total T_3, and T_3-by-RIA tests should be abandoned because they are inaccurate and unreliable as gauges of thyroid function.[63] Physicians in Britain, South Africa, and several other countries did so years ago. In contrast, the richest and "most medically-advanced" nation in the world is still adversely influencing people's thyroid health in a penny-wise, pound-foolish way by either sticking to these cheaper, outdated, inaccurate tests, or by limiting the blood testing to a single, indirect, fallible measure of all types of thyroid malfunction—the ultra-sensitive TSH test.

The most common conventional way to diagnose hypothyroidism is with an ultra-sensitive TSH that is elevated beyond the so-called "normal reference range." For most labs, the upper limit of the normal range varies from about 2.5 at the low end, to 4.0-5.0 mU/L at the high end. This is thought to reflect the anterior pituitary's sensing of inadequate thyroid hormone levels in the blood or in its own cells, which would be consistent with grades 1 and 2 primary hypothyroidism. This range will undoubtedly diagnose the severest grades of primary hypothyroidism but it is far too limited a measure, and large numbers of patients who have some other form or degree of hypothyroidism will be missed. This strategy will fail to detect secondary and tertiary hypothyroidism because TSH is not elevated in these conditions. (Psychiatrists and nutritional medicine practitioners find secondary and tertiary hypothyroidism to be far more common than endocrinologists think. This is because endocrinologists fail to measure the accurate T_3 level often enough to detect an abnormality.) The conventional strategy will also fail to detect the "euthyroid sick" syndrome which, by definition, has a TSH level in its normal range. And, it will miss grade 3 primary hypothyroidism unless one realizes that a TSH level in the upper half of its "normal range" identifies this condition.

Some Modern Conventional Myths About Diagnosis and Treatment

In the author's opinion, the current conventional approach is used because of the following nine errors of thought. The first four myths are widely held concerns that persist in the conventional medical community regarding *the TSH and its role in the diagnosis and treatment of hypothyroidism.* They join five other misperceptions.

The Myths.

(1) "An elevated ultra-sensitive TSH level is almost always required before a diagnosis of hypothyroidism can be made." (This myth was addressed in the previous section.)

(2) "'Over-suppression' of the TSH almost always means that excessive treatment, or hyperthyroidism *de novo*, is in place." Normally, the anterior pituitary will secrete enough TSH to maintain adequate thyroid hormone levels. When this fails to occur, either grade 1 primary or secondary hypothyroidism is considered to be present. There seem to be subtle (conventionally-termed "subclinical") failures of the anterior pituitary to produce sufficient TSH in response to low thyroid hormone levels. These failures cannot be explained solely by the traditional form of secondary hypothyroidism (secondary to a pituitary tumor or outright pituitary failure, as in Sheehan's Syndrome: postpartum hemorrhage or infarction of the pituitary gland). Secondary hypothyroidism can also be due to a TSH-specific hidden hypopituitarism. Failure to produce sufficient TSH could also be due to tertiary hypothyroidism, in which the thyrotropin-releasing hormone (TRH) from the hypothalamus fails, for poorly understood reasons, to stimulate the anterior pituitary to secrete adequate amounts of TSH.

(3) "Because the new ultra-sensitive TSH test is a very sensitive and accurate *test* for measuring *the TSH level*, this new test for TSH is always or usually the correct yardstick by which to measure *the function of the thyroid hormones T_4 and T_3."* This is an unconscious, unintentional "sleight of hand." The assumptions are that if the ultra-sensitive TSH is low-normal, adequate amounts of T_4 are being converted to T_3 in the pituitary receptors; and that if the ultra-sensitive TSH is below normal, excessive amounts of T_3 are being formed from T_4 in those receptor cells. There does not appear to be any evidence

that the pituitary gland—or any organ or tissue for that matter—can convert T_4 to T_3 at any greater rate than that which is reflected in the serum FT_3 level. Anyone who routinely measures the serum FT_3 level will observe that it is often *low*, even when the TSH level is low-normal or below normal, and even in the absence of identifiable pituitary or hypothalamic disease. Some of these cases are so-called "euthyroid sick"/non-thyroidal illness syndrome cases, and some are subtle secondary or tertiary hypothyroid cases without known disease involvement of either the pituitary or the hypothalamus. Other cases may be any combination of these two forms of hypothyroidism, or of non-thyroidal illness hypothyroidism, or of grade 3 primary hypothyroidism.

The TSH is an *indirect* gauge of T_4 and T_3 activity; *it depends on its own integrity of function and not only on the relative highs and lows of the two thyroid hormone levels*. Most of us realize this truth when there is known hypopituitarism or hypothalamic malfunction. But, we don't recognize that it is *also* true in subtle/occult pituitary and hypothalamic failure, and in the hypothyroidism that is now increasingly recognized as a frequent accompaniment of non-thyroidal illness or the "euthyroid sick" syndrome.[13][19][47] It is incorrect to state that the FT_4 and FT_3 levels are inconsequential. High or high-normal levels would indicate that the high or high-normal TSH is not even due to hypothyroidism but to lab error, stress, a spurious high TSH, or some other condition. This is another example of why it is *always* necessary to measure FT_4 and FT_3. Measuring the TSH level can occasionally be eliminated with a patient who over-suppresses the TSH even when FT_4 and FT_3 are *not* elevated. But in my opinion, FT_4 and FT_3 can *never* be dispensed with.

(4) "The normal range of TSH is approximately 0.4-4.2 mIU." Where is the evidence for this range? *Many* patients with TSH levels of 1.0-4.5 (and lowish-normal FT_4 and FT_3 levels) have classic hypothyroid symptoms—and they *virtually always* respond to thyroid hormone treatment with dramatic resolution of these symptoms and a quantum leap in their sense of well-being, mood, energy, bowel function, memory, etc.[82] Sometimes, patients with these mild degrees of thyroid hypofunction can be taken off the thyroid treatment after 3-12 months without relapsing. Perhaps the treatment, which causes a period of rest for the thyroid gland and which is known to reduce autoimmune antibodies,[70] enables the gland to recover at least temporarily.

(5) "It is not necessary to measure the FT_3 level because FT_4 usually converts adequately to FT_3." This is simply not true. (Many of the myths involve the FT_4 and FT_3 serum levels and the "inappropriateness" of T_3 in the treatment of hypothyroidism.) FT_4 *often*—more often than not, at least in depressed and chronically fatigued hypothyroid patients—*does not* convert sufficiently to FT_3,[15][22][31][38][76] neither in humans nor in laboratory rats.[24] Routine measurement of FT_3 (by the accurate dialysis method) *whenever* screening for, or monitoring treatment of, hypothyroidism will quickly confirm this.

(6) "It is not a good idea to treat with a combination of T_4 and T_3 because the FT_3 level is so unstable and inconsistent that one cannot obtain useful information from measuring it, potentially leaving the patient open to the wrong dosage [usually too much] of T_3." All that is required to invalidate this objection is to *always* prescribe a dosage for any T_3-containing preparation that is to be taken *twice- to thrice-daily*. Taking the two split doses *after* breakfast and dinner assists in stabilizing the FT_3 level by slowing its absorption and thereby extending its duration of action. There seems to be no appreciable fluctuation of the FT_3 level when this simple dosing regimen is implemented. The 3x-daily regimen does not require after-food administration as the 8-hourly repetition of the T_3 easily maintains a consistent serum level.

(7) "The 'euthyroid sick'/non-thyroidal illness syndrome should never be treated with any thyroid hormone because it never involves a malfunction of the thyroid gland or hormones that may cause any symptoms." Once again, this is not accurate. Chopra[13] expands on this, and Palazzo and Suter's letter suggested that at least some "euthyroid sick" patients, even acutely ill ones in an intensive care unit, do *not* have adequate thyroid function. They believe the patients would probably benefit from increasing their thyroid hormone levels, especially T_3.[47] Finally, Leslie DeGroot has also joined the questioning of the prevailing dogma on this issue.[19]

(8) "T_4 is the only hormone that should be used in treatment; one should *never* prescribe a combination of thyroid hormones." Why not? If that is the only way to optimize *both* the FT_4 and FT_3 serum levels—and that is *usually* the case—what is wrong with treating with two thyroid hormones? The gland itself secretes both. The fact that it usually requires the prescribing of both hormones to optimize the

serum levels of T_3 and T_4, taken within the context of the rare use of that treatment approach, certainly gives one pause about the adequacy of the treatment of most patients in the U.S. (and in countries where no form of T_3 is even available such as, at last report, Australia, Israel and Spain!).

(9) "Keeping both the FT_4 and FT_3 levels at the high end of their normal ranges will cause osteoporosis." This concern was merited 30-50 years ago when much higher doses of thyroid hormone were used in the treatment of most cases of hypothyroidism. This author, however, has not observed this complication in over 19 years of his more aggressive approaches to treatment.[82] In fact, his treatment-optimized hypothyroid osteoporotic patients' bone density scans not only don't deteriorate from one year to the next but almost invariably *improve*, by statistically significant percentages, without the use of elindronate, calcitonin, or any other drugs. This means that actual "overtreatment" of hypothyroidism would have to be more substantial than is currently thought. Concurrent correction of other factors such as deficiencies of vitamins, minerals, other hormones, and amino acids seems to maintain and extend bone density even in the presence of optimal or "aggressive" treatment of hypothyroidism.

Exemplars of "Alternative" Approaches

Broda Barnes's book *Hypothyroidism: The Unsuspected Illness*[5] is used by many natural medicine physicians in the U.S. in their approach to hypothyroidism. The book suggests that 64 diseases are caused or aggravated by hypothyroidism (mostly undiagnosed), and that hypothyroidism afflicts approximately 40% of the population. The 40% figure seems high. But, if successfully treated grades 1 and 2 primary, all grade 3 primary, subtle forms of secondary and tertiary, and many cases of non-thyroidal illness hypothyroidism are added to the 10% of the population found in the health fair survey[53] previously mentioned who are either untreated or inadequately treated grades 1 and 2 primary hypothyroidism cases, the figure must surely jump to at least 20%—of which only a small percentage is being treated.

Two further controversial "alternative" physicians have also more recently become associated with a focus on T_3. The first is Dennis Wilson, MD, of Florida.[77] In the early 90s, he noticed that many patients with chronic fatigue and other similar symptoms had low basal body temperature, *a la* Broda Barnes, and low T_3 levels (actually low total T_3 levels, a less accurate depictor of the T_3 status than the FT_3 level, especially by the tracer-dialysis method). He dubbed this condition "Wilson's Syndrome." (The name is inappropriate because it is easily confused with Wilson's Disease, a disorder of copper metabolism named after a different physician a long time ago). Wilson treated his patients with a slightly longer-acting form of T_3 and reported that most of them improved significantly. He contended that the T_3 could often be discontinued after a few months and some of the patients would not relapse into the low T_3 state. This was presumably because the supply of T_3 had broken the "vicious cycle" of the low T_3 level causing a breakdown in peripheral conversion of T_4 to T_3. (It is possible that the action of 5'deiodinase is dependent on a certain threshold amount of T_3.) However, some patients—perhaps most—needed to stay on the T_3 treatment.

Other physicians find that these patients then have high-normal, above-normal, or way-above-normal FT_3 levels, and subnormal or low-normal FT_4 levels.[83] This would appear to be almost as unfortunate as the converse situation, commonly found in a conventionally-treated hypothyroid patient, in which the FT_4 level may be in or above the normal range but the FT_3 level is at or below the low end of its normal range. We say "almost as unfortunate" because T_3 carries out 90% of the thyroid function.[12] Having at least adequate T_3 would appear to be more important than having T_4 at an adequate serum level *if one has to choose between the two* (which, of course, is not the case). But, as mentioned previously, the cells of the brain may require the availability of plenty of T_4 for conversion to T_3, since T_4 is transported more briskly through the "blood-brain barrier." On the other hand, Escobar-Morreale et al showed that, at least in the rat, *some* additional T_3 needs to be available directly for optimal brain cell function to occur.[24]

The other physician currently promoting a controversial "alternative" approach to the management of hypothyroidism and thyroid hormone resistance is John C. Lowe, DC of Texas. He has, particularly, found high doses of T_3 very beneficial in cases of euthyroid fibromyalgia.[44] Because the patients were euthyroid and their symptoms were relieved by supraphysiologic T_3 dosages that did not produce thyrotoxicosis, the researchers concluded that the patients had peripheral resistance to thyroid hormone. Lowe has found that a substantial percentage of these euthyroid cases are improved or put into remission by T_3 therapy. He uses T_3-only therapy with euthyroid patients, but with primary and central hypothyroid patients, he generally uses T_4/T_3 combination preparations with either desiccated hog tissue or synthetic hormones. One of his research partners, Richard Garrison, MD, until his untimely death in 2007, was engaged in a Veterans' Administration approved study on the effects of T_3 in Gulf War Syndrome, a condition thought to be related to chronic fatigue syndrome and fibromyalgia (which are often present in the same patients). He was using hyaluronic acid, which has been found to be a marker for fibromyalgia[79] and hypothyroidism,[84] as a gauge of the improvement, if any, brought about by T_3 in Gulf War Syndrome.

Presentation of the Hypothesis

The current conventional and "alternative" approaches do not allow for optimal, comprehensive diagnosis and treatment. The author proposes a new approach that is more logical and perspicacious, and which imitates the basic physiology of thyroid function. This approach includes attention to grade 3 primary hypothyroidism, subtle non-obvious forms of secondary/pituitary and tertiary/hypothalamic central hypothyroidism, and many cases of non-thyroidal illness hypothyroidism. The author submits that most cases treated by the current standard approach are in fact under-treated, and he proposes a logic-supported treatment approach that eliminates this situation.

Sensitive Diagnosis

Although this is not a report of any actual findings on his part, it is fair to say that the author has observed dramatic clinical improvement in thousands of patients whose thyroid status was previously regarded as normal (based on the older tests or on a single TSH level, or a combination of the two) when he has boosted patients' free T_3 levels, and often the FT_4 levels as well. This new approach always utilizes the FT_3 and FT_4 diagnostically, as well as the ultra-sensitive TSH serum level. The TSH is given the new normal NACB (National Academy of Clinical Biochemistry) reference range[81] of 0.4-2.5 mU/L, but levels between 1.0-2.5 mU/L are also considered for treatment as cases of grade 3 primary hypothyroidism, secondary, tertiary, or non-thyroidal illness hypothyroidism if the FT_4 and FT_3 levels are no higher than the lower quarter of their reference ranges. Readings between 0.01 and 0.40 are tolerated in patients who have other causes for a low TSH level, as discussed above. Understandably, the suppression of a TSH that was not elevated without treatment is not going to be in the low end of its normal range on optimal FT_4 and FT_3, but will be well below that level and possibly even as low as 0.01 mU/L.

A significant number of patients have a TSH level below 1.0 but their FT_3 and possibly FT_4 will be below normal. These are cases of secondary/pituitary or tertiary/hypothalamic central hypothyroidism,[49] or of "euthyroid sick"/non-thyroidal illness syndrome.[46] These individuals should receive supplemental thyroid hormone therapy, especially if they have serious conditions like depression, chronic fatigue syndrome, obesity, or early dementia that are dependent on good thyroid hormone function for their reversal. There are far too many of these extremely vulnerable patients to ever believe that the TSH alone is an adequate screening tool.

In both diagnostic screening and treatment monitoring since 1989, measuring both the FT_3 and FT_4 serum levels on all patients usually shows a large disparity between the two measures.[82] Unless patients had life-threatening or cardiac-arrhythmic illnesses (in which low T_3 serum levels may have been life-saving by keeping their metabolism and/or heart rate low), including T_3 in their treatment invariably enabled patients to lose their classic hypothyroid symptoms just as described in the literature[4][21][22]—something study patients had not been able to do with T_4-only treatment even when the FT_4 level had been pushed to the maximum or beyond.[15] In most cases, it is important for both FT_4 and FT_3 levels to be optimized with whatever combination of T_4 and T_3 is necessary in treatment. This objective necessitated the use of both T_3- and T_4-containing preparations in the management of the vast majority of all hypothyroid patients. Gelenberg reported the same phenomenon in a psychiatric newsletter.[31]

There are currently four categories of hypothyroidism that are often not being diagnosed as such and therefore go untreated:

(1) grade 3 primary hypothyroidism;
(2) subtle secondary/pituitary hypothyroidism without identifiable pituitary tumor or disease;
(3) subtle tertiary/hypothalamic hypothyroidism (in

depression, chronic fatigue, and other chronic illnesses); and

(4) many cases of non-thyroidal illness/"euthyroid sick" syndrome hypothyroidism (in which the low FT_3 and sometimes FT_4 levels are counter-productive and not life-saving).

The remaining categories, grades 1 and 2 primary hypothyroidism, are usually diagnosed and treatment is embarked upon, but these patients are very often under-treated mostly due to excessive concerns about cardiac arrhythmias and osteoporosis/osteopenia being caused or aggravated by high-normal thyroid replacement. In most of the studies that suggest these concerns, researchers did not perform the accurate dialysis free T_3 test—or *any* T_3 test.

A 1999 paper by Bunevicius et al shows the superiority of T_4 plus T_3 over T_4-only treatment of 33 hypothyroid patients in a double-blind crossover study.[11] The fourth author, Arthur Prange, is one of the several American psychiatrists who have published articles on the great benefit of T_3 in refractorily depressed patients.[33][74] It is likely that the benefit of the combination approach used in the 1999 study would have been even greater if the FT_3 and FT_4 levels had both been optimized, rather than a fairly arbitrary amount of the previous T_4 treatment simply being substituted by a functionally equivalent amount of T_3. Nevertheless, this is a landmark paper. The Bunevicius study, and those of Escobar-Morreale et al,[24] Chopra,[13] DeGroot,[19] Saravanan et al,[56] Appelhof et al,[2] and the present paper, as well as the popular books by Arem[4] and Shames and Shames,[59] and the lay patient-advocate view by Mary Shomon on the website Thyroid.About.com, should all help to revolutionize the treatment of hypothyroidism—despite the cautionary editorial in the same issue of the *New England Journal of Medicine* that published the Bunevicius paper.[68]

Further evidence of the shift toward including T_3 in the assessment and treatment of the various forms of hypothyroidism is provided by yet another paper published in 1999. The multi-center Italian study, "Evaluation of the adequacy of levothyroxine replacement therapy in patients with central hypothyroidism," reported that "both FT_4 and FT_3 serum levels . . . are necessary for a more accurate disclosure of over- or under-treated patients."[27]

Even Toft, one of the giants of thyroidology in the modern era and who initially reacted so negatively to the publication of the Bunevicius et al paper, largely showed himself to be open to a reassessment of the idea of the addition of T_3 to T_4 treatment. In an abstract published in April 2002, he stated, *inter alia*, the following: "The first treatment for hypothyroidism, introduced at the end of the 19th century, was animal thyroid extract which contained both T_3 and T_4. Because of variable potency it was widely replaced by synthetic T_4, from the 1960s, in high doses of 200-400 ug daily to compensate for the lack of T_3. The development of TSH assays showed that a dose of T_4 of 100-150 ug daily was usually adequate to restore serum TSH to normal [*sic*]. Because a suppressed serum TSH has been shown to be a risk factor for osteoporosis, atrial fibrillation, and most recently for excess cardiovascular mortality, there is a consensus that the correct treatment of hypothyroidism is a dose of thyroxine which restores euthyroidism and maintains both T_4 and TSH in their respective reference ranges. However, a significant minority of patients only achieve the desired sense of well-being if serum TSH is suppressed. Furthermore, patients rendered hypothyroid following treatment of thyrotoxicosis, and taking a dose of T_4 which maintains a normal TSH, gain more weight than those who do not become hypothyroid. Studies in hypothyroid rats suggest that it is only possible to restore universal tissue euthyroidism using a combination of T_3 and T_4. Patients in whom long-term T_4 therapy was substituted by the equivalent combination of T_3 and T_4 scored better in a variety of neuropsychological tests. *It would appear that the treatment of hypothyroidism is about to come full circle.*"[69] (Italics mine.)

Toward the end of 2003 there was a rash of papers, in the *Journal of Clinical Endocrinology and Metabolism* in October[57][72] along with an editorial by Kaplan et al,[40] and an article in the *Journal of the American Medical Association* in December,[14] "showing" that the substitution of T_3 for some of the T_4 in T_4-treated hypothyroid patients produced no benefit. But, these study patients' T_4 and T_3 serum levels were even less optimized than those of the 33 patients in the Bunevicius et al 1999 paper.[11] In addition, they often ended up on a lower total daily intake of thyroid hormone (T_4 and T_3 combined) than they had originally been receiving when T_4-only was their treatment. This is no way to try to prove the futility of T_3 treatment—not only for primary hypothyroidism patients but even less so for patients who have one of the other types of hypothyroidism (either as the sole cause of their hypothyroidism or as an additional cause of their total hypothyroid picture). In these latter types of hypothyroidism there is a strong tendency for the dialysis free T_3 level to lag behind the dialysis free T_4 level. This is partly because of a lack of TSH (which drives the conversion of T_4 to T_3), but may also be due to peripheral interference with the 5'-deiodinase conversion of T_4 to T_3.

It is telling that the Kaplan et al editorial[40] indicated a marked note of despair that an ideal treatment for all the symptoms of hypothyroidism will ever be found! Considering the flawed assumptions on which the editorial and the articles were based, it is not at all surprising to me that optimal treatment is an elusive goal to these researchers and opinion-makers! If they would simply switch their focus from "optimizing" TSH to truly optimizing the dialysis free T_4 and free T_3 serum levels, they would achieve, as I have, this laudable goal in virtually all their patients.

The holy grail publication pendulum has already started to swing back toward evidence for the efficacy of the addition of T_3 to T_4 treatment. We see this in two articles published in the first half of 2005, Saravanan et al[56] in February (697 primary hypothyroid patients) and Appelhof et al[2] in May (141 primary hypothyroid patients). The Appelhof paper compared the outcomes for two different ratios of T_4 to T_3, 5:1 and 10:1. It is notable that the patients receiving the higher amounts of T_3 reported the most satisfaction with their results, especially in weight loss. Unfortunately, both studies were still operating under the flawed assumption that whatever amount of T_3 was added to any patient's treatment, an equivalent amount of T_4 had to be subtracted. Using my approach, the T_4 dosage would have been increased in many patients due to its level still being suboptimal. Because of the feedback loop: $T_3 \rightarrow TSH \rightarrow T_4$, the addition of T_3 would have actually lowered the total amount of T_4 available, thus requiring additional amounts.

Optimal Treatment

The issue is: What is the best substance with which to treat these patients? The approach being advocated here, used successfully since 1989 in over 5,000 patients,[82] has the goal of optimizing the free serum levels of *both* the T_3 and T_4 thyroid hormones (measured by the dialysis methods). The physician should use in treatment whatever combination of both thyroid hormones produces this result (and that includes T_4 alone). This is true regardless of whether the treatment results in a TSH level below its normal range. If such a result occurs, it simply means that the patient's TSH feedback loop is not functioning properly, or else it would not be suppressed below normal when the T_4 and T_3 thyroid hormone levels are *not elevated*!

Unless the FT_3 level in a new case is significantly higher than the FT_4 level, it is not optimally helpful to treat with T_4-only replacement. If the patient has a high TSH level (TSH drives T_4-to-T_3 conversion) and still cannot directly produce enough T_3 from his or her gland and from the conversion of T_4 to T_3 peripherally, then that patient will not convert enough T_3 from T_4-only treatment after the TSH level drops.

The conventional approach to the treatment of hypothyroidism assumes that T_4-only preparations convert peripherally to T_3 in fairly standard amounts and at fairly standard rates. If that does not occur, it is considered to be because of extrathyroidal illness "which is of no concern to the physician charged with correcting *thyroid* dysfunction." But, the clinical experience of always measuring free T_3 and free T_4 serum levels shows that the assumed scenario is not true for the majority of patients. At least 80% of my patients have required some T_3 in treatment (always prescribed for 2 or 3 times/day dosage) in addition to T_4 for their free T_3 and free T_4 serum levels to be optimized.

Consistent measuring of both the FT_3 and FT_4 blood levels in all hypothyroid patients who are on *T_4-only therapy* will very rapidly dispel the myth of adequate conversion (as well as the myth of "extrathyroidal causes" of low T_3 levels). A certain *minority* of hypothyroid patients do convert enough T_4 to T_3 at a sufficient rate for T_4-only treatment to be effective in producing an adequate FT_3 serum level. However, as I said above, the majority of patients require some combination of T_3 and T_4 to optimize FT_3 and FT_4 levels. Once these levels are optimized, the patients' health and performance improve.

Optimizing both the FT_3 and FT_4 levels usually requires: a combined T_4/T_3 preparation, separate T_4 and T_3 preparations, or a combination of T_4 *and* a T_4/T_3 preparation. Desiccated whole hog thyroid (e.g., Armour Thyroid) is a good, relatively inexpensive starting point for the fixed combination T_4/T_3 treatment. Since it contains the short-acting T_3 hormone, it should always be prescribed to be taken *after* breakfast *and* supper (in the twice-daily regimen) to reduce the rapidity of onset and prolong the duration of action. The major shift in thinking for most physicians is to recognize that desiccated thyroid hormone should be taken *not* just once a day, but twice daily after meals. An alternative would be dosages taken three times daily (every 8 hours) without regard to meal times. If desiccated thyroid alone does not optimize both hormones' free levels, additional T_4 (or less often T_3) treatment can be added in order to achieve the goal. If synthetic thyroid hormones are used exclusively, an estimated amount of T_4 would be taken once daily along with an estimated amount of T_3 to be taken twice daily after breakfast and supper (or as described above, every 8 hours without regard to meal times).

Once optimal T_4 and T_3 hormone replacement has been achieved, the ultra-sensitive TSH remains useful as a gauge of optimal thyroid function only if it is still in the low end of its normal range, or it may go below the low end of the range (down to 0.01 mU/L). If this occurs, thyroid function will have been optimized by the yardstick of both the TSH level *and* the dialysis FT_4 and FT_3 levels. As one who has both a personal and a perfectionist interest in *optimal* thyroid function rather than "normal" function, my view is that the only satisfactory optimization is the one just described. It remains to be decided, in certain rare cases in which the TSH needs to be suppressed below 0.01 mU/L for the dialysis FT_4 and FT_3 levels to be optimized, whether to accept suboptimal free T_4 and free T_3 levels or a sub-0.01 mU/L TSH level. My own preference would be for the latter, except in frail or cardiac-arrhythmic patients.

Monitoring Treatment

The TSH, FT_3, and FT_4 serum levels are measured 4-8 weeks after treatment has begun. The interval depends on whether T_4-only or some combination of T_4 and T_3 is being used. Because the longer half-life of T_4 necessitates a longer period before its "steady state" (and that of the T_3 it is converted to) is reached, the TSH, FT_4, and FT_3 levels should only be obtained after 6-8 weeks of continuous treatment if T_4-only is used. After testing and according to the results, doses of thyroid hormones are then adjusted.

In order to optimize hormone replacement in otherwise healthy young or middle-aged patients, FT_3 and FT_4 levels should be near the upper end of the laboratory normal reference ranges (the upper one-third). Lower levels (in the middle one-third of the ranges) should be the goal for cardiac-arrhythmic and/or elderly or frail patients. Once stabilized, the levels need only be checked annually or semi-annually unless clinical indicators demand earlier re-testing.

A small number of large or overweight thyroid hormone resistant patients, *usually women*, may need up to 6-9 grains of Armour Thyroid per day (or the equivalent of thyroxine, counting 0.1 mg of T_4 as 1 grain; or a combination of the two). These patients seem to represent some form of thyroid hormone resistance syndrome.[51]

Patients who already take Armour Thyroid in once/day dosages should be advised to split their doses immediately according to the twice- to thrice-daily formula described in several sections above. After the splitting, the only change will be in their FT_3 levels. If patients have been on the same daily intake of the combined T_4/T_3 treatment for at least 5 weeks before the splitting of the doses, their serum FT_3 levels can be measured 48-72 hours after the splitting (T_3 needs only 48 hours to achieve its steady state level).

Testing the Hypothesis

The above diagnostic criteria and treatment methods should be applied to a large clinical trial using excellent measures of patients' actual functioning in their lives (including jobs and relationships, and social and leadership qualities). In this way, the hypothesis could be tested and assessed to be true or false.

Implications of the Hypothesis

It goes without saying that undiagnosed, untreated, and under-treated cases of hypothyroidism would cause massive morbidity, mortality, and suffering. If found to be true, the hypothesis would lead to the following conclusions: Many of the hyperlipidemias,[17][23][29][34] myocardial infarctions,[28][41][42][64] affective disorders,[18][22][32][33][38] dementias,[35][37] obesities, hair losses, peripheral neuropathies,[48] and some psychoses;[43][50] and in many cases, conditions such as hypertension,[28][41][64] chronic fatigue,[67] impotence,[7][52][78] immune suppression,[58] and chronic constipation, could easily be ameliorated. Furthermore, if thyroidologists, endocrinologists, and other physicians were to incorporate the principles of the hypothesis, *millions* of patients would improve the diminished quality of life that they currently lead.

Serious Thoughts About Iodine

It is well known that the original cause of most cases of hypothyroidism was iodine deficiency. In an effort to deal with that issue in a public health, cost effective manner, iodized salt was substituted for non-iodized salt on all our grocery store shelves. This measure has taken the edge off the extent of the iodine deficiency of yesteryear—although not by any means completely, as good measurements of both organic and inorganic iodine levels in patients' blood or urine would show. But has anyone in thyroidology stopped to recognize that we have actually substituted many *more* cases of autoimmune thyroiditis/primary hypothyroidism for the relatively fewer cases of iodine deficiency hypothyroidism that existed previously?

Could the mechanism for this phenomenon be that we used the wrong form of iodine—inorganic instead of organic—as a food supplement, and that this harsh form of iodine actually damages the thyroid tissue enough to trigger our immune systems to react against it? I believe this is a question that, at the very least, deserves serious consideration and investigation. I have laid out this case to David Brownstein, Guy Abraham, and Jorge Flechas, and also to the Past-President of The Endocrine Society, Len Wartofsky. To date, none of them has responded.

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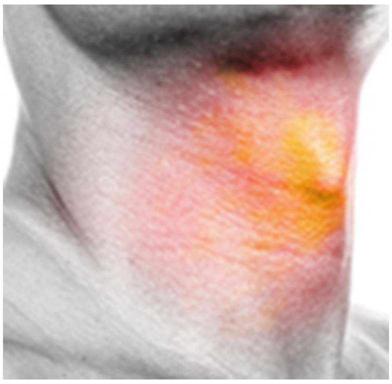

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Thyroid Science 3(1):1, 2008
Invited Editorial

Redefining Hypothyroidism: A New Paradigm

Bo Wikland, MD*

(Full Text Free in pdf format)

*Hötorget Medical Centre, Sveavägen 13, SE-111 57 Stockholm, Sweden,
Contact: bo.wikland@comhem.se

KEYWORDS: fine needle aspiration cytology, hypothyroidism, thyroid autoimmunity, thyroid autoantibodies

Introduction by Dr. John C. Lowe

Editor-in-Chief

We recently invited Dr. Bo Wikland of Stockholm, Sweden to write an editorial for *Thyroid Science*. We did so because of the importance of the research he and his colleagues have conducted and reported. That research involves what they term "subchemical hypothyroidism." After reading their reports in *The Lancet*, I noted this condition and its importance in a *Thyroid Science* editorial.

Here, however, Dr. Wikland himself explains to us the importance of this condition and how to diagnose it. His recognition of this clinical phenomenon and the solution he provides for patients suffering from it is nothing short of momentous. He calls for a paradigm shift in the diagnosis of hypothyroidism. In my view, such a shift is imperative: It is crucial to incalculable numbers of hypothyroid patients recovering their health, and it will be of vital interest to clinicians who are truly concerned about the well-being of these patients.

As Dr. Wikland explains, the shift he calls for entails including tissue evidence of thyroiditis in patients' diagnostic workups. This evidence can supplement biochemical test results that have indicated that patients are hypothyroid. Or, more importantly, the tissue evidence can show that the patient is hypothyroid when biochemical testing often fails to do so. Dr. Wikland uses and recommends tissue morphological evidence from "fine-needle aspiration cytology." (An informative website that explains find-needle aspiration cytology is available at no cost.) This diagnostic procedure has the potential to rescue patients whose clinicians would otherwise deny them the thyroid hormone treatment upon which their health and well-being depend. We are grateful to Dr. Wikland for composing his invited editorial for *Thyroid Science*.

Wikland, B.: Redefining Hypothyroidism—A Paradigm Shift. *Thyroid Science,* 3(1):1, 2008.

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Thyroid Science 3(1):H1, 2008 www.ThyroidScience.com *Hypotheses*

What is Optimal Treatment of Hypothyroidism? A Matter of Clinical Common Sense

Bo Wikland, MD*

*Hötorget Medical Centre, Sveavägen 13, SE-111 57 Stockholm, Sweden *Contact:* bo.wikland@comhem.se

Keywords: Autoimmune thyroid disease • B_{12} deficiency • Clinical symptoms • Criterion of optimal treatment • Fine-needle aspiration • Free T_4 • Hypothyroidism • Quality of life • Subclinical hypothyroidism • Thyroid antibodies • TSH

There is general agreement that autoimmune affection is a major cause of thyroid imbalance. Hypothyroidism is conventionally defined according to biochemical variables. Patients whose values for the first-line tests TSH and free T_4 are considered, respectively, "high" and "low," are judged hypothyroid. A substantial proportion of patients have "high" TSH but "normal" free T_4; these patients are said to have "subclinical hypothyroidism" (notwithstanding clinical symptoms).

Demonstration of thyroid autoantibodies is an important manifestation of thyroid autoimmunity. In cases with a strong suspicion of hypothyroidism, the autoantibodies warrant treatment with thyroid hormone, as discussed previously in this publication.[1]

In the investigation of patients with chronic fatigue, B_{12} deficiency must be ruled out at an early stage. This condition is not infrequently concomitant with autoimmune thyroid disease. If the B_{12} deficiency is not corrected, optimal supplementation of the thyroid condition is difficult to achieve.

Clinicians seeing patients with suspected hypothyroidism, whose first-line tests fall short of attaining levels conventionally considered compatible with hypothyroidism or "subclinical hypothyroidism," are left uneasy. Could hypothyroidism really be confidently excluded on these grounds?

In the diagnostic work-up of the constantly tired patient, there is a step beyond the conventional biochemical/serological thyroid analyses. That step is a direct approach to document autoimmune assault on the thyroid. It is called "fine-needle aspiration (FNA) cytologic examination." The additional diagnostic and therapeutic yield of FNA over conventional first-line tests is considerable.[2][3] We have demonstrated autoimmune lesions of lymphocytic invasion of the gland in clinically hypothyroid patients whose presenting levels of TSH were less than 1 mU/L (and ranging up to 30 mU/L, with a median of 3.8 mU/L). The patients' clinical responses to thyroid medication were equally favourable regardless of their baseline TSH levels.

Now, that clinical hypothyroidism with cytomorphological evidence of autoimmunity has been found in patients with perfectly normal TSH levels, and that supplementation with thyroid hormone is indicated, which management protocol is optimal? Obviously, guidelines based on TSH criteria (restoration of TSH to "normal") are no longer valid. In an excellent survey, Anthony Toft[4] presents a sensible and balanced view on this topic (applicable to patients diagnosed by FNA as well). He states, "It may well not matter whether . . . therapy in patients with primary hypothyroidism results in a serum TSH concentration of less than 0.1, 1.5, or 3.7 mU/L, as long as a sense of well-being is restored."

Why do many patients on thyroid medication achieve wellness only when their TSH is low or suppressed? One explanation is that, in these patients, the TSH signals trigger and maintain autoimmune activity; and, consequently, a low TSH is a prerequisite condition for the patients to have a satisfactory quality of life.

What, then, is the criterion of optimal treatment of patients with hypothyroidism? The answer is not to perfunctorily restore the TSH to "normal." The answer is openness to patients' individual needs to restore thyroid balance—a matter of clinical common sense.

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Is There a Thyroid-Cortisol-Depression Axis?

Frank King Thompson[Δ,ϒ]
(Full Text Free in pdf format)

[Δ] *Director,* Fallbrook Medical Research Foundation
[ϒ] *Contact:* Frank King Thompson, 2414 Via La Orilla, Fallbrook, CA 92028, USA
760-728-6090, fkthompson@fmrfoundation.org

ABSTRACT. How thyroid hormone therapy relieves many patients' depression has not been clearly elucidated. The relief of depression may result from a thyroid hormone-induced drop in cortisol and consequent potentiation of brain neurotransmitters. If so, it is possible that patients whose depression is underlain by high cortisol levels are most responsive to thyroid hormone therapy. If so, then the antidepressant effects of selective serotonin and norepinephrine reuptake inhibiting drugs may act partly through thyroid hormone effects on brain cortisol.

Key Words. Depression, cortisol, thyroid hormone, neurotransmitters, serotonin reuptake inhibitor, norepinephrine uptake inhibitor.

Thompson, F.K.: Is There A Thyroid-Cortisol-Depression Axis?
Thyroid Science, 2(10):H1, 2007.

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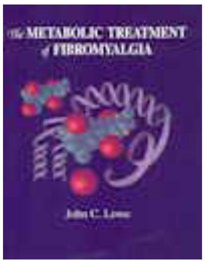

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Myofascial Pain

Dr. John C. Lowe

We can define the term "myofascial pain" in at least two ways. First, it may be pain that actually arises from skeletal muscle and/or its connective tissues. Second, it may be pain that we only perceive arises from these tissues.

Pain that *Actually* Arises from Myofascial Tissue

When myofascial pain *actually* arises from a myofascial tissue, the tissue is either damaged or there is a threat of damage. A myofascial trigger point is a good example of threatened or real damage to myofasicial tissue. At a trigger point, an excess of the transmitter substance acetylcholine induces a contraction of muscle fibers.

When the contraction increases the pressure inside the muscle beyond some threshold, local arteries, veins, and lymph channels are compressed. Compression of veins will reduce the elimination of metabolic wastes from the tissue region.

If the wastes accumulate, their high concentration will lower the firing threshold of local nerves (specifically, type C and A delta fibers). The receptors of the nerves respond to pressure. The increased pressure, caused by the contraction, within the tissue activates the nerves. The resulting increased nerve flow into the spinal cord and brain are termed "nociceptive" because humans perceive it as unpleasant or painful.

The increased nerve flow activates two types of nerves cells within the spinal cord that can intensify the adverse conditions of the local tissue. The signals from the tissue activate sympathetic nerves, and an increased flow of signals through these nerves to the tissues induces contractions of arterioles. When the arterioles contract, arterial blood flow to the local tissues further decreases.

Also, the signals from the tissue activate alpha motor nerves. Signals passing through these nerves back to the involved myofascial tissue increase the contraction of muscle. The increased contraction heightens local muscle pressure. The increased pressure further reduces blood flow through arteries and veins, intensifying the adverse process even further.

If muscle cells are destroyed by this process, muscle proteins are replaced with an accumulation of connective tissue. We then say that the tissue is "dystrophic." The perception of pain in this case arises first from changes in the myofascia that threaten damage, and second, from actual damage of the tissue.

Pain that is *Mainly Perceived* to Arise from Myofascial and Other Peripheral Tissues

The best example of an individual who only *mainly perceives* that her pain arises from peripheral tissues is the patient with severe fibromyalgia.

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Fibromyalgia patients have an increased perception of pain. They appear to do so because of two biochemical changes in the central nervous system: (1) an increase of substance P, and (2) a decrease of norepinephrine. (Studies have failed to show the serotonin deficiency in the central nervous system that some researchers, such as I. Jon Russell, hypothesized. So, the available evidence doesn’t support the related hypothesis that fibromyalgia patients’ increased pain perception is underlain by a low central nervous system serotonin deficiency. For practical purposes, the serotonin deficiency hypothesis of fibromyalgia is falsified.) The increased substance P and low norepinephrine levels in fibromyalgia can be induced by too little thyroid hormone regulation of central nervous system cells.

The increased substance P augments the flow of nociceptive nerve signals into the dorsal horns of the spinal cord. At the same time, low secretion of norepinephrine into the dorsal horns (by the endings of descending inhibitory nerves) results in a failure to properly inhibit incoming nociceptive nerve signals. As a result, an excess of nerve signals from myofascial and other peripheral tissues enter the spinal cord and ascend to the brain. The excess signals give rise to the perception of pain. It is important to emphasize that the increased pain perception in fibromyaglia doesn’t result from damage or the threat of damage to peripheral tissues. Instead, the patient perceives pain because her central nervous system pain modulating system is impaired.

This isn't to say that fibromyalgia patients don't often have some pain from threatened or real damage to myofascial and other tissues. They do, and when they do, their perception of this pain is usually more intense that of a person without fibromyalgia. But fibromyalgia patients tend to perceptive pain from nerve signals that wouldn't be painful if their central nervous system pain-modulating system worked properly.

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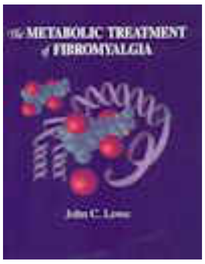

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Myofascial Therapy

Dr. John C. Lowe

Myofascial therapy is any treatment technique or procedure that either prevents or relieves symptoms and signs related to the myofascial tissues. This is a broad-brush use of the term allows for various treatment.

Most practitioners and patients today use the term "myofascial therapy" as a generic term to describe physical treatment methods applied to skeletal muscles and their connective tissues. These tissues, as a anatomical and function unit are referred to as "myofascia" or "myofascial tissues."

The earliest use of the term myofascial therapy appears to have been in the 1950s by an osteopathic physician in Beverly Hills, California. Travell and Simons, in the famous Trigger Point Manual, used the term sparingly. In the early 1990s, Dr. John C. Lowe used the term in 20 or so articles published in chiropractic publications. He also promoted use of the term in seminars across the USA. Soon, other writers and practitioners within chiropractic and massage therapy followed suit.

The term "myofascial therapy" originally referred to the diagnosis and treatment of myofascial trigger points. During the 1990s, however, some practitioners and patients began using the term in a more generic sense. They began using the term to refer to most any form of bodywork in which practitioners address their patients' soft tissue problems. Accordingly, some people use the term to refer to different types of massage, rolfing, and neuromuscular technique (Europe) or therapy (USA). As long as the practitioners of the different approaches address their patients' myofascial tissues, the term seems to properly apply.

Some people use the term myofascial therapy to refer to *any* form of soft tissue treatment. It's debatable whether this is always proper. For example, a practitioner (such as a chiropractic sports physician) may focus treatment on injured ligaments. In this case, to apply the term myofascial therapy seems imprecise. It does so because ligaments aren't properly classified as muscle (myo) or the connective tissue coverings of muscle (fascia). But one could argue in the other direction: Through reflexes, an injured ligament may induced protective muscle contractions, and the contractions may become a clinical problem. For example, they may cause a biomechanical imbalance. Or they may compress and activate myofascial trigger points. If speeding the healing and repair of the ligament helps relieve the myofascial complication, it seems proper to classify the treatment of ligaments as myofascial therapy.

Opinions as to the proper use of the term "myofascial therapy" will differ. Probably the best policy is for each person who uses the term to stipulate what he or she means. Otherwise, the term may in general have little meaning. On drlowe.com, we use the term in a very broad sense. We certainly include physical treatment techniques, such as myofascial trigger point therapy. But we also include any biomechanical, psychological, or biochemical treatment that can relieve patients of myofascial pain and dysfunction. This is consistent with the use by authorities such as Richard Finn, MTPM; and Dr. Leon Chaitow; and Judith Walker DeLany.

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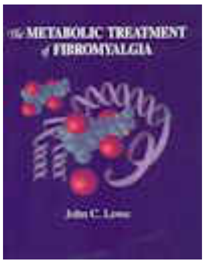

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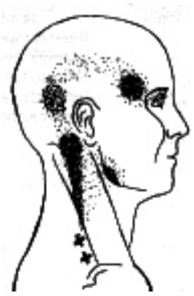
Myofascial Pain Syndrome

Dr. John C. Lowe

In *Myofascial Pain and Dysfunction: The Trigger Point Manual*, vol.1, the authors explain that the term "myofascial pain syndrome" has been used in two different ways. Some practitioners use it to refer to any regional pain syndrome of soft tissue origin. Other practitioners, such as Travell and Simons, use the term to refer to sensory, motor, and autonomic symptoms caused by myofascial trigger points.[1,p.5] The most common sensory symptom is pain. A motor symptom is muscle weakness, and an autonomic symptom is tearing. The term "myofascial pain syndrome" is best reserves for this second definition.

The authors of the *Trigger Point Manual* define "myofascial trigger point" this way: "A hyperirritable spot in skeletal muscle that is associated with a hypersensitive palpable nodule in a taut band." They also write, "The spot is painful on compression and can give rise to characteristic referred pain, referred tenderness, motor dysfunction, and autonomic phenomena." [1,p.5]



The drawing to the left is from a manual I wrote and illustrated in 1989 (*The Purpose and Practice of Myofascial Therapy*, Houston, McDowell Publishing Co.) The drawing shows two myofascial trigger points in the right upper trapezius muscle. When compressed, these trigger points refer pain to the shaded and stippled areas on the right side of the neck and head. Most people have *latent* trigger points in this muscle.

The term "latent" means that the trigger points (1) increase tension in the muscle and restrict range of motion, but (2) they don't refer pain until compressed. They can become compressed a clinician palpates the muscle or when the tension of the muscle increases during activity such as carrying a purse or brief case with the right hand. We can experience referred myofascial pain by squeezing the muscle between the fingers of the left hand.

Psychologist Ron Melzack (who co-authored the gating theory of pain) points out that trigger points may form at the site of even minor injuries. He writes that major procedures such as cordotomies may fail to relieve pain. ("Cordotomy" is division of nerve tracts of the spinal cord. The division may be made by techniques such as incision or radio frequency coagulation.) On the other hand, simple procedures such as trigger point treatment techniques may produce sudden, remarkable recovery and a return to work.[2,p.111]

Trigger points are the easiest-to-confirm mechanism of pain, yet the most neglected.[3] We can document trigger points by thermography and algometry. For most clinical purposes, however, this isn't necessary. When properly trained, the practitioner can locate myofascial trigger points through manual palpation with a highly degree of reliability.[4,p.33-36]

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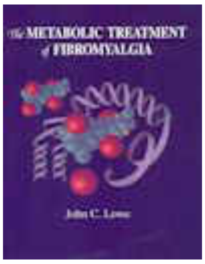

Welcome to Our Section on Myofascial Pain Syndromes, Trigger Points, & Myofascial Therapy

Latest Updates to drlowe.com

Dr. John C. Lowe

On the Internet, I've read a great deal of false information about myofascial pain syndromes, trigger points, and myofascial therapy. The most unfortunate—and resoundingly false!—bit of information is this: "There is no effective treatment for myofascial pain, so if you have it, you'll just have to learn to live with it."

Quite the contrary! An expert myofascial therapist can quickly inactivate the myofascial trigger points of most patients. And inactivating the trigger points abruptly stops the patients' pain.

Ingenuity is required to free some fibromyalgia patients from trigger point pain, or at least to keep the pain from recurring. For example, most fibromyalgia patients with trigger point pain must recover normal metabolism before their trigger point pain is kept at bay. But even before these patients normalize their metabolism, skilled myofascial therapists can at least keep the patients' trigger point pain under control.

Myofascial therapy was for many years one of the mainstays of my clinical practice. I know from that clinical experience that for relieving pain, few treatment methods equal the pain-relieving potency of myofascial therapy. Because of this, I believe patients, doctors, and therapists should have access to scientifically accurate information of practical value on myofascial pain syndromes and their treatment. For this purpose, several years ago, I added this section to drlowe.com. My earnest hope is, as it was then, that the information will enable patients to get effective treatment for their myofascial trigger points.

If you have pain or other symptoms that you believe are caused by myofascial trigger points, I strongly recommend that you use two resources to find a qualified therapist.

National Association of Myofascial Trigger Point Therapists (NAMTPT)

One resource is the NAMTPT (www.MyofascialTherapy.org). The organization has a referral network through which you may be able to find a certified therapist in your area. You can reach the organization through email (info@myofascialtherapy.org) or phone (1-800-845-3454.)

Richard Finn, CMT, PTS, CMTPT

Carol Finn, MTPT

If you live in the Pittsburgh, PA area or can travel to it, you can avail yourself of the treatment by Richard or Carol Finn. I have known Richard and Carol for many years, and I've had the extraordinary experience of being treated by him. Richard is Director and an Instructor at the Pittsburgh School of Pain Management. He is one of the world's most knowledgeable experts on myofascial pain and its treatment.

I haven't yet been treated by Carol, but I plan to. Considering that she was educated and trained by Richard, along with other faculty members at the School, I expect that her skills, like his, are truly exceptional. As well as caring for human beings, she specializes in treating canines. In doing so, she improves their range of motion and relieves any discomforts that arise from their myofascial tissues. You can contact the Finn's for appointments through the School, and you can reach Carol on her cell phone at 412-266-2359.

Pittsburgh School of Pain Management (PSPM)

PSPM (www.PainSchool.com) PSPM offers the only training program of its kind in the United States, educating students in the basic science foundations of myofascial abnormalities and their treatment, and training students so that they can begin their career in relieving the pain, other symptoms, and dysfunction that myofascial trigger points can cause.

The school is recognized by the National Association of Myofascial Trigger Point Therapists. It is licensed by the Commonwealth of Pennsylvania, and is accredited by the Accrediting Bureau of Health Education Schools.

Graduates are eligible to sit for the certification exam provided by the Certification Board for Myofascial Trigger Point Therapists. Many graduates go on to receive recognition as Fellows or Clinical Associates with the American Academy of Pain Management.

Contact information:
1312 East Carson Street
Pittsburgh, PA 15203
Main number: 412-481-2553
Fax: 412-481-3279
E-mail: painschool@earthlink.net

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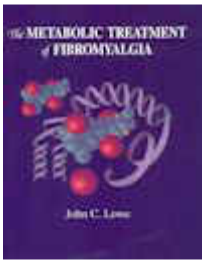

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Ultrasound Treatment of the Fibromyalgia Patients' Trigger Points

Dr. Gina Honeyman-Lowe

(Paper presented at the French Fibromyalgia Association
of Région Rhône-Alpes, Grenoble, France, May 6, 2000)

For most patients who don't have fibromyalgia, ultrasound can be an effective therapeutic modality for several soft tissue conditions. The conditions that respond well to ultrasound include dystrophy, taut bands, hypermyotonia, and active and latent trigger points. In our experience, the soft tissue condition most common and troublesome to fibromyalgia patients is myofascial trigger points.

Myofascial trigger points in most FMS patients respond well to ultrasound. This is especially true when the ultrasound is used in combination with stripping massage, moist heat, and spinal adjusting.[1] As well as desensitizing trigger points and stopping pain referred from them, ultrasound has a pleasant, soothing effect on most fibromyalgia patients.

The protocol for treating fibromyalgia patients with ultrasound is basically the same as that for with patients who don't have fibromyalgia . The main difference is that many fibromyalgia patients have a lower tolerance for ultrasound intensity. With some fibromyalgia patients, the intensity of the ultrasound must be reduced below the intensity that most other patients find comfortable. Fibromyalgia patients may have to be treated with very low ultrasound intensity, perhaps fewer than 0.1 watts/cm^2. Similarly, muscle stripping usually has to be done very gently, with the amount of manual pressure properly adjusted according to constant feedback from the patient.[4]

Ultrasound is especially effective because of its multiple effects in soft tissues. No other modalities appears to have this set of tissue effects.[3] The effects include the following. First, ultrasound energy is converted into heat at tissue surface boundaries due to waves meeting intra- and intercellular resistance. This property is unique to ultrasound. The greatest effects of treatment occur where two unlike structures interface. Second, the fine vibrations from the ultrasound exert a micromassage effect on the treated tissues. Ultrasound can also alter the structure of scar tissue by breaking down the collagen fibrils with specific action on interstitial cement and by disengaging collagen cross bindings. Third, ultrasound has several chemical effects in tissues. For example, ultrasound stimulates streaming of calcium ions from cells, increases gaseous exchange and oxidation, and liquefies some cellular gels. Forth, ultrasound waves can induce the absorption of exudates and precipitates and can decrease edema. Fifth, ultrasound can inhibit impulse conduction in type C nerve fibers. Sixth, ultrasound waves may also cause microdestruction of tissue deposits such as calcified hematomas and osseous proliferations. Last, but very importantly, ultrasound waves may trigger enkephalin production, producing a mild sedative effect.[2]

Administering ultrasound in the continuous setting is preferable that in the pulsed setting. The effects of ultrasound listed above are induced only minimally by pulsed ultrasound. To get a therapeutic effect with pulsed ultrasound (except with edema) requires a prolonged treatment time.

The treatment protocol for myofascial trigger points includes positioning the patient comfortably so there is a slight passive stretch of the muscle to be treated. Some fibromyalgia patients are uncomfortable maintaining the same body position for long during treatment. These patients should be permitted to reposition themselves whenever necessary so that they remain as comfortable as possible. However, the position the patient assumes should permit the muscle being treated to be relaxed, in a slight degree of stretch, and accessible to the ultrasound. The temperature of the room should be warm enough to prevent chilling of the tissue being treated.

During treatment with continuous ultrasound, the ultrasound transducer (head) should be moved continually to prevent excess heat from accumulation on the face of the ultrasound head and in the skin. However, the ultrasound head must be moved slowly during treatment, about 1.25-to-2.5 cm/second. The maximum depth of penetration of the sound waves is approximately 5 centimeters. When treating trigger points, the usual intensity setting is 1.0-to-1.5 watts/cm^2. Contraindications are the same as for any other heat-producing modality.[2]

The size of the area to be treated is approximately 5 cm^2 in diameter.[7] Attempting to treat too large an area will diminish the effectiveness of the treatment. Confining the ultrasound treatment to a small enough area allows the energy to be concentrated enough to reach the taut band and trigger point and have a strong therapeutic effect.[6] The clinician should apply ultrasound to the trigger point for 4-to-5 minutes using a circular motion with the ultrasound head. The head should be moved at a speed of 1.25-to-2.5 cm/second. The intensity should always be adjusted to patient comfort. A warm, soothing effect for the patient is optimal.[5] By the time the patient feels the soothing effect, the trigger point is usually desensitized. If the trigger point was referring pain before treatment, the referral has ceased. If the point was only locally painful, this too has usually ceased. However, the taut band will remain tender to pressure for a time. Feedback from the patient is essential for proper treatment. If the patient perceives excessive heat, the ultrasound intensity is too high and must be decreased.

Also, sound waves that are too intense for the individual patient can activate nociceptive mechanoreceptors in the taut band that houses the trigger point. This will cause pain referral from the trigger point. Again, the intensity should be decreased. Mild pressure may be applied with the sound head to obtain a muscle stripping effect. If the stripping action is painful to the patient, the clinician should decrease the amount of pressure or discontinue the stripping action.

Next, the clinician should apply moist heat for 5-to-8 minutes. The heat increases circulation by reducing sympathetic vasoconstrictive impulses to the taut muscle band that contains the trigger point. The heat also reduces alpha motor signals to the muscle, further decreasing the tone of muscle fibers around and in the trigger point region. After the use of heat, the clinician should passively stretch the muscle being treated. The stretching elongates the muscle fibers of the taut band, disengaging the actin and myosin fibers, and permitting normal circulation to resume.[7]

Finally, the patient's spine should be *gently* adjusted. Any force applied during the adjustment should be calibrated to the fibromyalgia patient's lower tolerance. Adjusting fixated spinal joints usually relaxes the patient and provides a sense of well being. However, adjusting spinal joints that are segmentally related to the muscle containing the trigger point can be especially effective. Adjusting segmentally-related spinal joints reduces motor activity in the involved muscle and decreases its sympathetic innervation.[8]

The patient should be instructed in home care consisting of the use of moist heat and gentle stretching of the involved muscles. For some patients, home treatment is more effective after the intake of a mild analgesic.[7]

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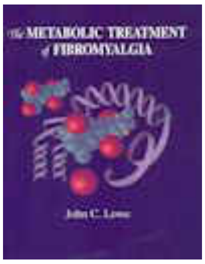

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Continuous Ultrasound in the Treatment of Myofascial Trigger Points: An Opinion*

Courtney Taylor-Robbins, P.T.

*Reprinted from
The Journal of Myofascial Therapy, 1(4):12, 1994.

Recently, I read a research report by Hong, Chen, Pon, and Yu.[l] They reported the results of their study of the effects of four therapeutic modalities commonly used by physical therapists and other practitioners who treat myofascial trigger points. The modalities they tested included stretch and spray, moist heat, ultrasound, and deep pressure soft tissue massage. The results are somewhat problematic for me because they are highly inconsistent with my clinical experiences.

These investigators compared the relative effectiveness of the four modalities. It is the outcome of this comparison that I was puzzled over. The investigators wrote that all four modalities were effective in the treatment of myofascial pain syndromes. They induced an immediate increase of pain threshold of active myofascial trigger points. They reported that deep pressure massage therapy was more effective than the other modalities in reducing the tenderness of active trigger points immediately after therapy. They also reported, "The stretch therapies [including spray and stretch and deep pressure massage] are more effective than thermotherapy [hydrocollator and ultrasound] in obtaining an immediate increase in pain threshold for myofascial pain treatment."[1,p.50]

I've treated patients' trigger points for over 10 years, and I've used extensively each of the four modalities tested in the Hong, et al. study. For some five years, I wasn't certain whether one modality worked better than the others. I worked diligently to master the use of each, and neither seemed to consistently work better than another.

In 1990, however, I attended a workshop taught by Dr. John C. Lowe.[2] That weekend, Dr. Lowe demonstrated the use of ultrasound to treat trigger points. According to the principles of ultrasound treatment he taught, my results with ultrasound were relatively ineffective for several reasons. I'd: (1) used pulsed rather than continuous mode, (2) moved the transducer at too fast a rate over the trigger point, and (3) failed to place the patient so that the muscle containing the trigger point was stretched somewhat during the ultrasound application.

At the workshop, I had some doubts about the wisdom of his advice. But when I used it back at my office, I found that what he had confidently asserted—that in 99% of cases, when applied properly, continuous ultrasound can stop an active trigger point from referring within 4.5 minutes—was precisely correct. My results dramatically improved, and as I've continued to refine my ultrasound technique, I've come to agree

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completely with Dr. Lowe: that continuous ultrasound is the most potent procedure available for stopping pain and other symptoms mediated by trigger points.

Of course, ultrasound is not a sole treatment for trigger points. I stretch the muscle as I apply ultrasound. After the ultrasound, I apply some soft tissue manipulation (a combination of ischemic compression and stripping massage). Next I apply moist heat, and then I have the patient actively stretch the muscle. Certainly these additional therapeutic procedures contribute to the treatment outcome, but without the ultrasound application, the sequence of other procedures is far less effective. I know this because the detailed progress notes I've kept on patients over the years I've treated for trigger points has allowed me to compare the results of the different protocols I've used. It is these learning experiences that make the results of Hong, et al. a little off base to me. When I read the study, I was actually startled at the results. I carefully read the paper, especially the parts describing how ultrasound was applied. The study was well done, and my assumption was that ultrasound must have been applied correctly. When I closely considered the technique used in the study, the conclusion I came to was that deep soft tissue massage seemed to be more effective because the ultrasound transducer (head) was moved too rapidly. The investigators pointed out that the ultrasound head was moved 3 to 5 cm (1.18 to 1.97 inches) per second.

I'll contrast Lowe's technique with that used in the Hong et al. study. This will serve to emphasize the critical differences—and similarities—in technique. Hong and colleagues wrote: "The ultrasound deep heat therapy was applied to the upper trapezius area of approximately 40-50 cm2 with the [trigger point] at the central portion. The ultrasound dosage was set at 1.2-1.5 watt/cm^2 for 5 minutes, as is usually recommended for soft tissue therapy to a small body part. The speed of the circular movement of the ultrasound applicator was constant and slow, at a rate of approximately 3-5 cm per second evenly applied on the treatment area, so that the patient always felt warm during therapy."[1,p.44]

When I studied the report of Hong et al., I found several consistencies with the technique I've found highly effective. First, the dosage of ultrasound is within the range I've typically found effective, 1.2 to 1.5 watts/cm^2. In addition, five minutes wasn't far off the average of four and one half minutes Dr. Lowe has reported.[3] But the tissue area included in the five minute treatment (40 to 50 cm2 or 15.75 to 19.69 inches squared) is far too wide to be highly effective. One change I made in my ultrasound technique at Dr. Lowe's recommendation was to concentrate the ultrasound application to roughly the 2 square inch area of skin overlying the trigger point. This allows maximum concentration of the ultrasound energy into the taut band containing the trigger point. Cover a wider area, and too little ultrasound energy may reach the taut band and trigger point to have a strong therapeutic effect. This particular difference may be the critical ingredient in the significant result I've found.

Other differences advocated by Lowe are: slight stretch of muscle being treated, deep pressure applied through the sound head, and maximum heat permitted through slow movement of the sound head. Dr. Lowe states that he arrived at his method through meticulous record keeping as to how patients responded to various ultrasound applications. He quotes Jaskoviak and Schafer[4,p.209] as stating, ". . . dosage levels, while limited, are made strictly on an empirical basis." In line with his, Dr. Lowe states[5] that his technique isn't based on unblinded studies, but on a sincere effort, with the benefit of algometry, to assess the trigger point desensitizing effects of various modalities.

I would like very much to see a controlled examination of the effects of continuous ultrasound used according to the method taught by Dr. Lowe. My prediction is that ultrasound should have a better showing than it did in the Hong et al. study.

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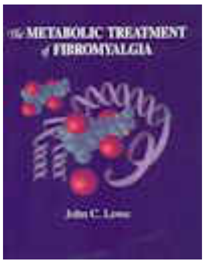

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Factors that Induce Fibrosis of Fascial Tissues

Dr. John C. Lowe

Traditionally, fascial tissue wasn't given as much attention as muscle by researchers and clinicians. This began to change in the early 1980s. From that time, a variety of practitioners have stimulated a great deal of interest in fascia. For the most part, the practitioners who've done so have been massage therapists and myofascial trigger point therapists. However, some physical therapists and osteopathic, medical, and chiropractic physicians have also made notable contributions. I'll refer to all clinicians who've contributed as "myofascial practitioners."

Health care consumers have benefited from this new interest in fascia. They've benefited because myofascial practitioners have provided relief from pain and dysfunction that result from abnormalities of fascial tissues. Patients and practitioners have often asked me about the factors that induce abnormalities of fascia. Because of this interest, I'm publishing here part of a presentation I delivered on audiotape in 1989 (*The Purpose and Practice of Myofascial Therapy*, Houston, McDowell Publishing Co). So what I'll talk about here are the three main factors that induce fascial abnormalities. They are (1) trauma, (2) chronic strain, and (3) immobility of fascial tissues.

Presentation

"Dr. Ida Rolf first began to promote her view in the 1950's that fascial tissues bind muscles and thereby impede adaptive, fluid motion of the body. Dr. Ray Nimmo, the chiropractor who championed trigger point therapy in the middle of the 20th century, didn't agree with her: 'I could not agree,' he wrote, 'with her explanation that the muscles were bound down by connective tissue and had to be broken loose. Connective tissue is too strong to be broken loose.' He also mentioned taking a class from D.C. McIntosh who taught a fascial release method. Nimmo wrote, 'We would palpate for tensed fascia (so we thought), then release it. Fascia got snagged up, [McIntosh] said, and we would release it. I couldn't figure how anything as slick as fascia could get hung up. What it was, of course, was tensed musculature.'

"When Nimmo made those comments, no one could do much more than conjecture about fascia. But today we have data that show Ida Rolf was right. Fascia does bind together, and it can be broken loose. Most of these data come from studies of either connective tissue injury or peripheral joint stiffness after periods of immobility. The studies aren't tantamount in depth nor breadth to the advanced and voluminous research that's been done on muscle. However, they do show that fascia can contribute in at least three ways to the woes of the myofascial patient. It can do this by becoming fibrotic when traumatized and when subjected to chronic strain. And it can do so by webbing together after periods of immobility. Any of these conditions can restrict mobility and pull myofascial attachments. The pulling can cause compression that impedes blood flow, produces energy-deficient contractures and trigger points, and sets off the adverse neurological ramifications I've talked about on other tapes in this series. I'll now describe how each of these factors—trauma, chronic strain, and immobility—can adversely affect fascia.

Trauma to Fascia. When fascia has been traumatized, it heals with a special type of collagen fiber called type III. These collagen fibers are laid down irregularly in all different directions. As the inflammation heals, the collagen fibers web the breach together. Applying cross-friction massage as the inflammation is resolving may help orient the fibers in a linear direction, with the stress lines of the tissue that's healing. If the fibers do become oriented to the stress lines, this may leave the body part normally mobile after the healing process is completed.

If the fibers are allowed to remain irregularly webbed, however, they'll contract and draw the tissue together toward its center. The contracted fibers will reduce the mobility of the myofascial tissue they're attached to. As the collagen fibers shorten, the pressure within the myofascial tissue will increase. The increased pressure will compress the arteries, veins, and lymphatics that course through the contracting tissue. This will create ischemia and, again, will induce energy-deficient contractures and trigger points.

Chronic Strain on Fascial Tissue. When fascia is chronically overloaded, myofascial pain syndromes can be exceedingly difficult to relieve. Chronic intermittent tension-loads on a myofascial tissue stimulates fibroblasts within the fascia to produce more collagen. Collagen therefore accumulates in the overloaded tissue. Fibrous tissue adapting this way to a mechanical load imposed on it is known as the "stretch-hypertrophy rule."

Most myofascial practitioners have palpated the effect of this stretch-hypertrophy. They've done so when they've palpated the hard, fibrous cords that run longitudinally along each side of the thoracic spine in the erector spinae muscles. Some practitioners call these cords "linear fibrosis." The fibrosis is especially prominent in the patient who projects his head out in front of the gravity line, as though leading his body with it when he walks. The upper thoracic erectors have to guy-wire the patient's head and neck---sometimes more, other times less. And this intermittent overloading stimulates the fibroblasts to synthesize and deposit so much collagen in the fascial layers that the erector muscles in some patients feel like steel cables.

I've found referring trigger points in these muscles in many patients. The trigger points are usually highly resistant to specific myofascial therapy. The treatment resistance suggests that the trigger points aren't just in contractured muscle. Contractured muscle is usually capable of releasing its tension, elongating, and thereby allowing inactivation of the trigger point. The treatment resistance of the trigger points instead implies that fibrous (or what some call "dystrophic") tissue is involved. We can induce fibrous, dystrophic tissue to release its pressure on hypersensitized nerves, and I'll explain how when I talk about treatment procedures and techniques on sides 9, 10, and 11 in this tape series.

Immobility. When fascia remains immobile for a time, perhaps as little as four weeks, cross-bindings can form between the molecules of its type I collagen. Type I is the normal collagen constituent of connective tissues. These cross-bindings reduce the flexibility of the fascia. They do this, at least in part, by restricting gliding between fascial sheets.

When connective tissue stays immobile, changes in the ground substance are perhaps more clinically important than the effects on collagen fibers. Protein-carbohydrate complexes in the ground substance bind water and give it its amorphous gel quality. (Researchers formerly called these water-binding complexes mucopolysaccharides, but they've changed the name to glycosaminoglycans.)

With immobility, the complexes gradually disappear from the ground substance. As a result, progressively less water is bound, and the bulk of the ground substance diminishes. As this happens, the collagen fibers come closer together. When the distance from one collagen molecule to another diminishes beyond some critical threshold, the molecules begin forming cross-bindings. As more and more molecules cross-bind, the involved connective tissue become less and less elastic. The tissue becomes less elastic because the collagen fibers and fascial sheets lose the ability to slide freely along one another. The effect is as though the tissue has lost some lubricating factor. But it appears that the collagen molecules of fascial sheets are actually tethered together.

Reduced mobility, or virtually immobility, of myofascial tissues is part of the problem with the patient who has heavy fibrosis of the upper thoracic erector spinae myofascia. As I said before, sustained guy-wiring of a forward-projecting head and neck chronically overloads these paraspinal myofascial tissues. This stimulates fibrosis. To worsen the problem, the upper thoracic spine has minimal mobility compared to the spine in the lower thoracic, lumbar, and cervical areas. And unless a person works at it, the paraspinal myofascia in the upper thoracic area is seldom stretched, torqued, or laterally bent. It just sits there. As fibroblasts deposit more and more collagen in response to the guy-wiring, the collagen appears to cross-link to form the thick cords we myofascial practitioners are so familiar with.

Most of us myofascial practitioners have patients who keep some—maybe even most—of their body parts practically immobile. That is, they use certain parts of their bodies in a guarded, tightly restricted range of motion. This is especially true of elderly patients. Many of these people have trigger points in these relatively immobile tissues, although most of the trigger points are "latent." This means, of course, that the trigger points aren't actively referring pain.

Travell and Simons (the authors of the famous *Trigger Point Manuals*) have pointed out that many elderly people have latent trigger points. They say these people seem to automatically restrict their range of motion to avoid activating and suffering from their trigger points. Based o principle, these elderly people's myofascial tissues are more likely to be fibrotic. This is likely because their reduced mobility permits type I collagen fibers to cross-link extensively throughout their bodies. The cross-linked collagen will exhibit physiological creep—that is, a steady pulling in on itself. At some critical point, the creep will cause the pressure within the tissues to increase to a critical point. At this point, blood flow will diminished, perhaps to the level of ischemia, and pain-mediating mechanoreceptors will be activated. At this time, the people will begin experiencing pain although they restricted their motion to avoid it. This is consistent with the view that the amount of collagen in connective tissues increases with age, making old animal meat tough. While the amount of collagen increases, the collagen fibers also develop extensive type I cross-linking.

As the years pass, many people restrict their body movements more and more. Eventually, their capacity for mobility becomes markedly reduced and they generally perceive stiffness. Mobility is important to tissue fluid exchange, and so their limited mobility seriously reduces blood flow. Blood flow in some circumscribed areas becomes so sluggish that the tissues become distinctly ischemic. At that stage, real trouble begins. First, energy-deficiency contractures can form and create trigger points. Far worse, though, the ischemia can cause muscle fibers to deteriorate. At the same time, fibroblasts become active and increase their output of collagen, bringing about some degree of myofascial fibrosis. The collagen fibers of this fibrotic area are likely to form cross-bonds that will tighten the tissue even more.

If the receptors of type C and type A delta nerves are trapped in this squeezing fibrotic tissue, the patient is likely to experience local tenderness and referred pain. These nerve responses are also likely to facilitate the segments of the spinal cord they enter. (Facilitation refers to a lowered threshold for neuronal firing.) This will stimulate motor fibers at the same level and cause hypertonicity of the associated paraspinal muscles. The nerve signals will also ascend to the brain stem and stimulate their reticular activating formations. The signals will also reach the thalamus. From there, relayed signals will stimulate cortical centers, disturbing thought and perception. The signals will also reach the basal (limbic) areas of the brain beneath the thalamus, which can produce disturbed emotions and interfere with the body's general homeostasis.

When relatively immobile myofascia lead to pain, freeing the patient from it may be difficult. Patients with fibrotic tissue aren't as responsive to therapy as patients whose source of pain is muscle contractures. There are at least two reasons for this.

First, fibrotic tissue can only be softened or stretched, and its cross-binds broken. First, in between therapy sessions, the tissue can shorten again unless the patient works diligently to keep it elastic. Diligence is required to counter the "physiological creep" I mentioned before. Second, many people who’ve minimized their movements to avoid myofascial pain have lost mobility and become generally stiff. They may lack the flexibility to cooperate in stretching muscles that house painful contractures and trigger points. For some of these people, relief can come only from therapies such as ultrasound and cross-friction massage that soften fibrotic tissues. Stretching the involved tissues, however, is fundamental to long-term improvement. If the patient isn’t able to effectively stretch because of severe inflexibility, he may require clinical care at frequent intervals.

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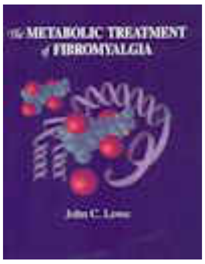

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Myofascial Genesis of Unpleasant Thoughts and Emotions: Its Neural Basis

Dr. John C. Lowe

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It is common for patients who are laden with chronic, intense myofascial constrictions to report severe mental agitation, fretting, insomnia, and other unpleasant thoughts and emotions. It is also common to hear these patients exclaim how profoundly relieved they are of their unpleasant thoughts and emotions after therapy relieves their constrictions and associated trigger points.

In the typical chiropractic office, both the doctor's and the patient's attention are usually on *physical* pain, and it's easy for the doctor to overlook the relation of the physical pain to the patient's emotional suffering. Even when a patient makes it clear that his emotions are being adversely affected by his physical pain, the doctor may be hesitant to deal with the patient's disturbed emotions. The doctor may feel, for example, that lengthy counseling may be needed and that this is incompatible with the time constraints of a chiropractic practice.

Unless the doctor has had special training in psychotherapy, it is probably best that he leave that form of treatment to clinicians who specialize in it. Giving encouragement, emotional support and practical advice is possibly the limit of what the typical doctor can reasonably provide in the way of *psychological* care. Fortunately, though, a great deal of patients' unpleasant thoughts and emotions are based on the state of their myofascial tissues; and the appropriate therapy is *not* psychotherapy but treatment the D.C. can deliver rapidly and effectively during the usual office visit.

In this paper, I briefly review the neuroanatomical relationship of constricted myofascia to unpleasant thoughts and emotions. Understanding how these relate can encourage the D.C.

to more often use his clinical skills to alleviate patients' emotional suffering by relaxing their myofascial constrictions. If a patient's emotional condition is of myofascial origin, the quickest, most effective, and most reliable way to give him thoroughgoing relief is through treatment directed to his myofascia.[1]

Myofascial Receptors

by Dr. John C. Lowe
Readers' Comments

Pain motivates most patients with myofascial constrictions and trigger points to seek clinical care. Receptors that give rise to the perception of pain are housed in the myofascia, and sustained myofascial constrictions and their trigger points tend to activate these receptors. Presumably, the adequate stimulus for the pain is an event in the myofascia that threatens or causes tissue damage.[2] Constrictions may cause tissue damage by compressing the arteries, veins and lymphatics that course through the constricted myofascia.

Myofascial tissue apparently contains few mechanoreceptors or thermoreceptors. It is, however, richly supplied with type A delta (Group III) and type C (Group IV) receptors. In man, type A delta fibers in skin" mediate sharp, stinging or pricking (epicritic) pain, and type C fibers in skin mediate poorly localized, dull, burning-aching (protopathic) pain.[3] In myofascial tissues, however, both type A delta and type C fibers give rise to delayed dull, agonizing pain felt to be deep and arising from a broad region of the myofascia.[4] Type C nociceptors respond to a wide variety of noxious stimuli: direct mechanical pressure, 5 per cent NaCl, weak acids, temperatures above 41 degrees centigrade or below 25 degrees centigrade, ischemia, and possibly serotonin. This type C response can be long-sustained.[5]

More than half the sensory fibers from myofascia are either type A delta or type C. It is significant that these fibers are highly responsive not only to mechanical and thermal stimuli, but also to chemical stimuli in their local environment. It has been hypothesized that high concentrations of certain chemicals in circumscribed areas of muscle and its fascia hypersensitize receptors and give rise to the trigger point phenomenon.[6]

A large percentage of the A delta fibers are metaboceptors; that is, they respond to chemical changes caused by muscular activity, such as increases in phosphate, lactate, and hydrogen ion concentrations.[7] The type C nociceptors have been shown to respond to bradykinin, serotonin, histamine, and potassium chloride.[8] It has also been shown that prostaglandin E2 and serotonin heighten the responsiveness of muscle receptors to bradykinin.[9] There is significant variation, however, in the responsiveness of types of muscle receptors to noxious chemical and mechanical stimuli. In general, type A delta and type C fibers are similar in their responsiveness to noxious chemical stimuli, although type A delta fibers have a lower threshold to potentially harmful mechanical stimuli.[10]

Intraneuronal stimulation of single afferent fibers in man produced responses in both type A delta and type C fibers.[11] Distinct sensations of dull pain and tension were perceived as coming from muscle. Neither sharp pain nor itch were perceived. Stimulation of less than half of the afferent fibers provoked pain felt in other areas of the body in addition to the pain felt in the myofascia itself. This referred pain phenomenon was not produced by stimulation of skin fibers.[12]

Spinal Cord Circuits and Pathways

Sensory signs from the myofascia that give rise to dull, poorly localized pain are transmitted through the older paleospinothalamic pathway. This "pathway provokes the powerful unpleasant affective and aversive responses of avoidance and activity. It accounts for much of the suffering associated with pain."[13] In this pathway, the primary sensory fibers conduct impulses from pain receptors in the myofascia to the posterior horn of the cord. There, the fibers synapses with secondary fibers that transmit impulses to the opposite side of the cord and ascend in the anterolateral tract to the thalamus.

The posterior grey horn of the spinal cord, through its complex circuitry, rearranges and modulates incoming sensory signals before sending them on to higher levels. Numerous mechanisms determine which incoming signals are sustained, which are potentiated, and which are nullified.

One mechanism is the complex interconnection of intrinsic fibers in the tract of Lissauer (situated at the outer tip of the posterior horn). As the rootlets of the sensory fibers penetrate the posterolateral aspect of the cord, most of the type A delta and type C fibers form a lateral group.

These small fibers either bifurcate or bend and then travel through one or two segments before they send collaterals to the substantia gelatinosa, located more centrally inside the posterior horn. The relatively short intrinsic fibers of the tract of Lissauer make up about 25 per cent of the tract.[14] They interconnect as many as five or six spinal segments.

This makes it possible for sensory signals from one segment to influence signals from other segments. And this intersegmental interaction appears to modulate to some degree the A delta and C sensory signals from the myofascia. Melzack's explanation of the Gate Theory has helped us to understand in part how sensation is modulated within these structures of the spine cord.[15][16]

Another important mechanism for altering incoming pain signals is a system of descending spinal pathways that strongly inhibit pain at the spinal level. This system is referred to as the serotonergic and noradrenergic spinal pathways.[17][18]

Subcortical Mechanism

It is at the subcortical level, in the brain stem and thalamus, that the sensory signals from constricted myofascia spark the neural mechanisms that give rise to aversive cognitive activity. As the pain pathways pass through the brain stem, some of their fibers terminate in its reticular activating area. As the pathways reach the thalamus, they separate into two separate pathways: the pricking pain pathway and the burning-aching pain pathway.

The pricking pain pathway terminates in the thalamus close to the tactile sensation fibers. There, it makes synaptic connection with fibers that transmit impulses to other parts of the thalamus and to the cortex. The close proximity of the pain and tactile fibers may account for the well-localized quality of pricking pain from cutaneous type A delta fibers.

Dull pain fibers, on the other hand, terminate in the reticular activating formations of both the brain stem and the thalamus. The reticular activiating system then conducts excitatory signals to all parts of the brain. The signals are transmitted from the thalamus to all areas of the cerebral cortex. They are also transmitted laterally into the basal regions around the thalamus, such as the hypothalamus and limbic system. These regions bring about emotional responses to noxious stimulation.

Guyton has pointed out that pain impulses, along with proprioceptive impulses, are the more potent stimuli in provoking arousal through the reticular system.[19] He has also clearly stated the effect of burning-aching pain signals: "The burning and aching pain fibers, because they do excite the reticular activating system, have a very potent effect for activating essentially the entire nervous system, that is, to arouse one from sleep, to create a state of excitement, to create a sense of urgency, and to promote defense and aversion reactions designed to rid the person or animal of the painful stimulus. The signals that are transmitted through the burning pain pathway can be localized only to very gross areas of the body. Therefore, these signals are designed almost entirely for the single purpose of calling one's attention to injurious processes in the body. They create suffering that is sometimes intolerable."[20] Korr has also pointed out that when noxious centripetal impulses are excessive, they
"produce . . . important psychological changes with potentially serious and

extensive changes in motor and visceral activity."[21]

Apparently even small isolated myofascial constrictions can give rise to great misery. Guyton writes of burning-aching pain signals, ". . . even weak pain signals can summate over a period of time by a process of temporal summation to create an unbearable feeling even though the same pain for short periods of time may be relatively mild."[22] Kimmel has pointed out[23] that spinal fixations also may give rise to centripedal stimuli that are subliminal but cumulative. Haldeman's[24] concurring viewpoint is that noxious signals from spinal joints are probably capable of stimulating the reticular activating system and providing generalized activation of the central nervous system.

Psychological Effects

Haldeman has written that insomnia is a well-documented emotional effect of somatic stimulation.[25][26] Jacobson found in many clinical observations and physiological studies [27,28,29,30,31,32,33,34,35] that disturbed thoughts and emotions are accompanied by electrically measurable heightened muscle tension. He also found that relaxing the tightened muscles relieved the unpleasant thoughts and emotions, even though the subjects had no knowledge of what the experimenters expected to occur.

As a result of his studies, Jacobson wrote: "There has been abundant evidence in these as well as in many other of our clinical studies that with the relaxation of such muscular acts, the entire process of thinking practically ceases for brief intervals." He also wrote: "It is true that maintaining general relaxation succeeds in markedly reducing, perhaps to zero, disturbed mental states."[36]

Jacobson demonstrated that heightened muscle tension (the basis of myofascial constrictions and trigger points) gives rise to unpleasant thoughts and emotions. He also demonstrated and stated that anxiety and muscle relaxation are physiologically incompatible.[37][38] Wolpe, considered the father of behavior modification, reiterated this incompatibility and reported that it was the basis of his effective clinical procedure called systematic desensitization.[39]

During this procedure, relaxation is systematically used to eliminate unpleasant thoughts and emotions that occur as conditioned responses to various stimuli. The efficacy of this extensively investigated procedure is additional clinical and experimental confirmation of Jacobson's conclusion that anxiety and general muscle relaxation can not occur simultaneously.

Conclusions

Sustained myofascial constrictions are likely to activate type C and type A delta sensory nerve fibers. The action potentials of these fibers travel through spinal cord pathways to the brain stem and thalamic reticular activating formations. From the thalamic reticular formation, signals are relayed throughout the brain and induce generalized physiological arousal. This arousal gives rise to behaviors whose aim is to remove the aversive stimulus.

The physiological arousal and behavioral activation are accompanied by unpleasant cognitions and emotions. As would be predicted from our understanding of the relevant neuroanatomy, when the myofascial constrictions and their trigger points are relieved, the unpleasant thoughts and emotions subside.

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Richard Finn, CMTPT
& the Institute of Medical Careers

Richard Finn is a certified myofascial trigger point therapist and is Director and Instructor at the Institute of Medical Careers. Mr. Finn is a foremost authority on myofascial trigger points and trigger point therapy. Those who study under Richard and his faculty receive the best training available in Travell and Simons-type trigger point therapy and more advance methods. We *strongly* recommend the Institute and Richard and Carol Finn to those who want to enter a helping profession of extremely value to those suffering from pain and other disorders. We also strongly recommend the Institute to those who are already in healing professions, such as therapists and doctors, who want to learn myofascial trigger point methods.

Training at the Institute includes the identification and control of perpetuating factors that can render patients treatment resistant. Training in perpetuating factors is essential if the therapist or doctor is to be highly effective in treating patients with myofascial pain syndromes. The Institute is the single best place we know of to acquire such training. It prepares students well to qualify through national certification as myofascial trigger point therapists.

Institute of Medical Careers
133 Jefferson Rd., Suite 101
Pittsburgh, PA. 15235
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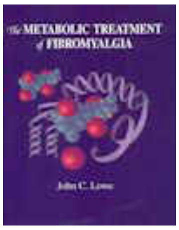
The Institute of Medical Careers (Pittsburgh School of Pain Management) is accredited by the Accrediting Bureau of Health Education Schools.

Trigger Point Therapist Referral Network

We often hear patients say doctors have told them there is no effective treatment for myofascial pain, and that the patients just have to learn to live with it. The doctors’ statements are patently false. Most patients with myofascial pain can overcome it, as long as they find practitioners trained and skilled at trigger point myofascial therapy.

It’s recently become much easier to find such a practitioner. A few weeks ago, we received notice of the new referral service of the National Association of Myofascial Trigger Point Therapists (NAMTPT). Through the service, patients with myofascial pain and dysfunction can find therapists certified by NAMTPT.

Certified myofascial trigger point therapists are educated and trained to accurately find the source of myofascial pain and to effectively relieve it. A small percentage of practitioners in other health care professions are good at



The Metabolic Treatment of Fibromyalgia
by Dr. John C. Lowe
Readers' Comments

A Guide to Metabolic Health
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myofascial trigger point therapy. But certified myofascial trigger point therapists are the only practitioners who exist strictly to provide the public with effective myofascial trigger point therapy.

If your doctor has told you there is no effective treatment for myofascial pain, and that you'll have to live with it, disregard the information as false. Then contact the NAMTPT referral service. They will help you find a certified therapist who can show you that in fact you don't have to live with myofascial pain. After you experience the relief, please let your doctor know. And be sure to give him or her the contact information for the referral service. Perhaps he or she will refer others to the service so that they, too, can get relief from their myofascial pain.

Trigger Point Therapist Referral Network
www.MyofascialTherapy.org
info@myofascialtherapy.org
1 (800) 845-3454

Joseph Hoane Ph.D., CMTPT
(973) 943-6129
joe@painpatterns.com
Clinic Address: 49 Howard Street, Verona, NJ 07044

I am a Trigger Point Therapist practicing in Verona, NJ, a location convenient for people in Essex, Morris, Bergen, Passaic, and Middlesex counties of New Jersey. Some patients come from Princeton, Trenton, Philadelphia and other places beyond the immediate area because no therapist with proper training is close to their homes. The goal of my practice is pain relief, improved posture, freedom of movement, and helping people understand and deal with the factors in their lives that may perpetuate their pain problems. I keep up-to-date by attending Continuing Medical Education (CME) courses and medical conferences each year. You can reach me at (973) 943-6129 or joe@painpatterns.com.

Dr. Joseph Hoane is a nationally certified myofascial trigger point therapist. He is also a member of the National Association of Myofascial Trigger Point Therapists and a member International Myopain Society

Jan Dommerholt, PT, MPS, FAAPM
Jan is a physical therapist and is President of Bethesdaphysiocare. He is a highly skilled clinician and expert in the identification and treatment of myofascial trigger points.

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A Tribute to My Friend and Research Colleague, Dr. Richard L. Garrison

We have posted my tribute to my friend and colleague, Richard Garrison, MD
to our Fibromyalgia Research Foundation website:
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Our Menu of Services: Long-Distance Consulting, Metabolic Evaluations & Treatment

by Tammy Lowe

We have a menu of my husband's clinical services and fees. We put the menu together so that you can avail yourself of some or all of the services, whichever best fits your budget. If you want to talk about Dr. Lowe's services, you can reach our me at 603-391-6061. If you prefer, you can email me at Tammy@drlowe.com. However, we also have a webpage where we describe our menu of services: Your Options for Metabolic Evaluations and Treatment.

The Lowe Clinic and Research Center
19 Long Springs Place
The Woodlands, TX 77382 USA
Tel (603) 391-6061 Fax (303) 496-6061 Tammy@drlowe.com

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1. IFM Endocrinology Symposium: A Heartfelt Thanks
2. Peripheral Thyroid Hormone Resistance—Not So Rare After All!
3. Our Menu of Services

Our Experience at the Institute for Functional Medicine Symposium: A Heartfelt Thank-You Note

Dr. John C. Lowe

For five days last week, my wife, Tammy, and I attended the 14th International Symposium on Functional Medicine in Tucson, Arizona. Sponsored by the Institute for Functional Medicine (IFM), this year's Symposium was titled, "21st Century Endocrinology: Thyroid and Adrenal as Sentinel Organs." On Friday, I gave a presentation on fibromyalgia and its relationship to thyroid disease.

In my presentation, I described finding the solution to the problem of fibromyalgia. I also touched on the treatment I developed for patients called "metabolic rehabilitation." I created, refined, and advanced this protocol over the past 20 years. So I was delighted to learn that among the six hundred physicians and other practitioners at the Symposium, many use metabolic rehab in their practices. They told Tammy and me that for the most part, they learned the protocol and the science it's based on from my book *The Metabolic Treatment of Fibromyalgia*.

But what was most heartening, scores of these practitioners sought out Tammy and me to express their thanks for my work, which many said they've followed for many years. So many of them shook our hands and said thanks that I felt something akin to what I feel at hearing John Denver's "rocky mountain high." The generous reception we received was immensely gratifying. I only wish that my editor and collaborator, Jackie Yellin, and her husband, Michael, could have been there to share the experience with Tammy and me. Jackie has worked step-by-step with me through those twenty ears, and Michael has always been our staunchest supporter.

It was the first time for Tammy to be among a large group of practitioners expressing what my research and publications have meant to them. Of course, each day at The Lowe Clinic and Research Center, she and Maureen, my clinical assistant, hear individual patients and doctors convey their thanks. But *en masse*, the comments of attending practitioners to Tammy and me were uplifting to us in a way that's hard to describe.

I want to mention here, as I did in concluding my presentation, a splendid person Tammy and I had the privilege of meeting and spending time with at Symposium. Our time with her was truly enriching. She is Misia Landau, Senior Science Writer at Harvard Medical School.

Not only is Misia delightful to be with, she's also an exceptional conversationalist and extraordinary thinker. She expressed her concern to Tammy and me that many patients—in my mind, perhaps most—are unable to get medical diagnoses that lead to relief from their suffering. But, she also told us she was encouraged and reassured by what she had witnessed at the IFM Symposium.

Misia attends many medical and scientific conferences and apparently finds them enriching. But at the IFM Symposium, she saw an exceptionally inspiring collective attitude of hope and enthusiasm among the attending practitioners. She was impressed by their eagerness to learn new, science-based methods to provide better medical care for their patients.

Along with Misia, Tammy and I were energized by the contagiously positive state of mind at the Symposium. We sensed this from everyone, from the IFM staff, to the medical faculty, to the attending clinical practitioners. We came away from the Symposium feeling so much kinship with this group that I'll be taking my place among IFM's membership.

We encourage everyone who reads drlowe.com to search the listing of IFM members when looking for local physicians, nurse practitioners, or other healthcare providers: http://www.functionalmedicine.org/findfmphysician/index.asp. We learned at the Symposium that IFM members are caring practitioners who stay abreast of cutting-edge medical science. And—of of immense importance to patients looking for answers to their health problems—they're willing to go "outside the box" on their patients' behalf in using that science.

I conclude this note by addressing the Symposium's staff, faculty, and attending physicians and other practitioners: Thank you so very much for taking the time to convey your thanks to Tammy and me. Your compliments came at a time when we were in need of a reviving experience, and you certainly gave us that—copiously. Your comments left me feeling that I've favorably touch the lives of many patients I'll never have the chance to meet personally. That gives me great solace, especially in view of the maddening obstructions of the last year. From deep in my heart, I thank you for your generous counterbalancing influence.

Peripheral Thyroid Hormone Resistance—Not So Rare After All!

Dr. John C. Lowe

In my book, *The Metabolic Treatment of Fibromyalgia*, the chapter on thyroid hormone resistance is the most extensive document ever written on the subject. When I surveyed the research literature to write the chapter, I included as many mechanisms of resistance that I could find. At the time, I proposed that peripheral resistance to thyroid hormone was not rare, as so many endocrinologists maintained.

Since the publication of *The Metabolic Treatment of Fibromyalgia*, researchers have found other possible mechanisms of resistance. Five Norwegian authors searched the latest literature and reviewed many of these other possible mechanisms in a new paper in the journal, *Medical*

Hypotheses.[1] (I received an advance copy of the paper, thanks to my dear friend and colleague Lyn Mynott, Chair of Thyroid UK.) These mechanisms include inhibitors of thyroid hormone transport across the outer cell membrane, furosamide (Lasix)-reduced binding of T3 to receptors in the cell fluid, carnitine interference with transport across the membrane of the nucleus, and a variety of toxins, other medications, and antibodies interfering at multiple cell sites.

I believe that readers will get the most benefit from this new paper after first reading my in-depth coverage of peripheral thyroid hormone resistance in *The Metabolic Treatment of Fibromyalgia*. Nonetheless, I recommend the paper to anyone interested in peripheral resistance to thyroid hormone. The reader should take special note of two of the authors' important points: First, peripheral resistance to thyroid hormone is *not* rare, as some researchers have claimed. And second, the TSH and thyroid hormone levels are useless for diagnosing this common disorder of impaired thyroid hormone action.

In their conclusion, the researchers state that what is needed is a method for measuring thyroid hormone action in the peripheral tissues. A method they mention is the resting or basal metabolic rate. They site a study, for example, in which researchers found that infants had low basal metabolic rates despite having normal TSH and thyroid hormone levels.[2] I couldn't concur more, as measuring the metabolic rate is one of the main diagnostic methods we use at The Lowe Clinic and Research Center.

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Our Menu of Services: Long-Distance Consulting, Metabolic Evaluations, & Treatment

by Tammy Lowe

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The Lowe Clinic and Research Center
1800 30th Street, Suite 216, Boulder, CO 80301 USA
Tel (603) 391-6061 Fax (303) 496-6200 Tammy@drlowe.com

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Persecution of Dr. Gordon Skinner by the General Medical Counsel of the United Kingdom

Monday, May 28, 2007, I received an email from Afshan Ahmad, PhD, Director of Vaccine Research International, Birmingham, United Kingdom. The organization is nonprofit and the headquarters of Dr. Gordon Skinner.

Dr. Skinner is a physician and scientist who's received honorary doctorates for his contributions in the field of virology. In addition, his brilliant mind—not compromised by conflicts of interest—observed that chronic fatigue syndrome wasn't a viral disease at all, as formerly thought. Instead, it is for the most part simply untreated or under-treated hypothyroidism. In my view, Dr. Skinner's current plight is an example of an all too recurrent tragedy: The earnest pursuit of truth is often rewarded with persecution by those whose self-interests and gain-through-conflicts-of-interest may be diminished by the unearthing of that truth.

Dr. Ahmad wrote to ask if I could come to the United Kingdom. The purpose would be to give evidence in Dr. Skinner's defense against the General Medical Council (GMC). The GMC is again trying to take away a physician's license to practice. The essential reason: because he's refused to restrict his patients to the life-ruining imposition on humanity called "T4-replacement" and instead, helped his patients get well.

Dr. Ahmad wrote of Dr. Skinner, "He holds you in high regard and feels that you have a great deal of knowledge and experience which would be useful in his defence." I, too, hold Dr. Skinner in high regard. I do so both for his scientific accomplishments and for the praise of his clinical care that I've heard from many patients in the U.K. I staunchly believe that for the GMC to deprive U.K. citizens of Dr. Skinner's safe and extraordinarily effective clinical care would be nothing short of an act of cruelty against those citizens.

The day that Dr. Ahmad's email came, I was thoroughly tied up with clinical responsibilities. When my wife, Tammy, read the email to me, I asked her to reply at once to Dr. Ahmad. Tammy wrote: "Thank you for your email and your request for Dr. Lowe's presence in London in defense of Dr. Skinner. Dr. Lowe is honored by your request and will do everything he can to travel to the U.K. for this important purpose. We will adjust his schedule to accommodate."

When Tammy and I got home from the clinic that evening, I was crestfallen when I checked and found that my passport had expired. We knew about the huge backlog for passport renewals, so we promptly tried to expedite renewal of mine. But as of today—like millions of other U.S. citizens—we have no idea whether I'll have the renewed passport in time to fly to England to testify on Dr. Skinner's behalf. (I've said quite enough in the privacy of our home about this example of the general ineptitude of the Bush Administration. So, I'll abstain from further comment here.)

Tammy appealed to a relative of hers who is special assistant to a senator, asking whether the senator could help us quickly get the passport renewal. The answer was, not unless my trip concerns U.S. national security. I feel that indeed the trip does involve national security; unfortunately for my passport renewal, it's the security of a large subset of citizens of another nation, the U.K.

If I cannot travel to England because of the passport problem, I'll testify on Dr. Skinner's behalf in any other way I can. As a start, I've written the article below. It calls on certain old-guard endocrinologists and their specialty to retract one of their health- and life-destroying false beliefs—a false belief that is serving in part as a ground for the GMC to persecute Dr. Skinner and to deprive U.K. citizens of his effective care.

I will be grateful to anyone else who writes or speaks in Dr. Skinner's defense. Those who do will, at the same time, be speaking out against a pernicious, commercially-based false belief of the endocrinology specialty. That false belief lowers the quality of medical care and forsakes the health and even the lives of hypothyroid patients not only in the U.K., but also in most other countries of the world.

Article by Dr. Gordon Skinner: "How I got interested in all this," based on a talk given to Chester MESH 20th June 1997: http://www.houghtongraphics.demon.co.uk/gordonskinner.html

A Letter to Patients from Dr. Skinner: http://www.thyroiduk.org.uk/thyroiduk_org/doctors/skinner/patient_prescription_letter.html

Thyroid UK's Comments on Dr. Skinner's Case: http://www.thyroiduk.org/
Scroll down to: "IMPORTANT INFO following Dr Skinner's IOP Hearing 26/02/07"

Dr. Skinner's book *Diagnosis and Management of Hypothyroidism* is for both patients and doctors. Throughout the book, Dr. Skinner's wit and delightful personality are manifest. His writing style is captivating. His patient orientation is characteristic of doctors of old who, unlike our modern medical extremist technocrats, used not only available technology, but their minds as well. I strongly encourage doctor and patients alike to read this extraordinary book by an extraordinary physician and scientist: http://www.thyroideducation.com/

Normal Metabolic Rates
Despite Suppressed TSH Levels:
Evidence in Support of Dr. Gordon Skinner

The endocrinology specialty has never publicly defended a double standard in its practice guidelines. That double standard goes something like the following: It's perfectly okay for thyroid cancer patients to take TSH-suppressive doses of thyroid hormone. After all, study-after-study has shown that these doses are harmless for the cancer patients. But, warns the specialty, if anyone else takes these doses, he is almost certain to lose bone and have an arrhythmic heart. Where is the scientific evidence for the specialty's double standard for thyroid cancer patients versus other hypothyroid patients? Where are the studies showing that thyroid cancer patients are exempt from harm from TSH suppression, but other hypothyroid patients are not? Despite long diligent searching, I can't find the evidence.

On the other hand, over the last twenty years, I've known countless hypothyroid patients who had never had thyroid cancer. But like thyroid cancer patients, they had for years taken TSH-suppressive doses of thyroid hormone. They did so because smaller doses left them suffering from hypothyroid symptoms. They had no choice—if they wanted to be well, which most of them were, they had to violate the specialty's treatment guideline and suppress their TSH levels with thyroid hormone. Just like thyroid cancer patients, these patients without cancer were free from any harmful effects. How do I know they were unharmed? Because I found that all the appropriate test results were normal: blood and urine biochemical tests, densitometry, cardiac assessments, and measurements of their resting metabolic rates.

The endocrinologist Dr. J. I. Hamburger apparently lacked experience with such patients when he wrote: ". . . no matter how unconvincing to some authorities, low-level overdosage of thyroxine may be harmful. Finally, it is consistent with the practical reality that there is no reason to think it necessary to give enough thyroxine to produce an undetectable sensitive-TSH value in the treatment of hypothyroidism."[2,p.122] Those countless hypothyroid patients I've known—who were well and totally unharmed by suppressed TSH levels—would beg to differ with Dr. Hamburger's opinion. I italicized that last word because this is all the endocrinology specialty ever offers to support its positions—no credible scientific evidence; just armchair opinion.

Maybe the reason the specialty won't speak out publicly about this double-standard guideline is that they really believe it's true. Maybe its members have never witnessed the evidence that disproves their false belief because they always comply with their own double-standard practice guideline. The guideline dictates that no hypothyroid patient without cancer can use TSH-suppressive doses of thyroid hormone. By steadfastly adhering to that guideline, members of the endocrinology specialty would never be able to see, through clinical experience, that the guideline is, in fact, false.

As I noted in *The Metabolic Treatment of Fibromyalgia*,[4,pp.881-2] in 1989 the Scottish endocrinologist Dr. Anthony Toft called a suppressed TSH a "thyrotoxic" level.[4,p.91] His statement means that if someone takes enough thyroid hormone to suppress his TSH level, then for certain, he'll consequently suffer from the syndrome of tissue overstimulation by thyroid hormone.[3]

For Toft to label a suppressed TSH level "thyrotoxic" was fine, as long as he qualified that his labeling was a hypothesis. But to state it as fact was irrational. Accumulating evidence has shown the idea to be wrong. Because of this, Toft should long ago have retracted the notion. Instead, his idea—at the time based on flimsy, tentative evidence and now scientifically refuted—has been shoved down the throats of practicing doctors as a scientific fact. The endocrinology specialty has intimidated practicing doctors into practicing only according to the refuted guideline—even if it destroys patients' quality of life and, in some instances, causes premature death.

Obviously, anyone can take too much thyroid hormone and become thyrotoxic. But except in rare cases, doses of thyroid hormone that are effective at relieving patients' symptoms aren't enough to poison them. These safe and effective doses, however, are often—if not usually—enough to suppress patients' TSH levels.

I just re-read a 1991 study that showed something interesting regarding this issue.[1] In the study, Japanese researchers measured the resting metabolic rates of thyroid cancer patients. For five weeks, the patients had been on TSH-suppressive doses of thyroid hormone. The researchers pointed out that measuring the resting metabolic rates of patients accurately tells us how thyroid hormone is affecting their tissues. They reported that their measures of the metabolic rates of patients with suppressed TSH levels showed "no enhancement of energy metabolism" (italics mine). They concluded, "From these findings, the post-operative TSH suppression therapy carried out at our department is considered to be justifiable from the viewpoint of energy metabolism."."

TSH-suppressive doses of thyroid hormone did not put these thyroid cancer patients into metabolic overdrive. Before long, I'll publish a study that shows the same result for hypothyroid and thyroid hormone resistance patients who don't have cancer. Not only does the scientific evidence show that TSH-suppression does not cause such patients to have bone loss or heart arrhythmias, as a rule, it doesn't even cause a rapid metabolic rate.

In 1989, the endocrinologist I mentioned above, Anthony Toft, wrote, [2,p.92] "There is increasing evidence that doses of thyroxine sufficient to suppress ppress thyrotroph secretion [of TSH] cause tissue hyperthyroidism in other organs such as heart, kidney, bone, and liver despite the lack of clinical evidence of thyrotoxicosis." Aside from the self-contradictory nature of this statement, Toft was wrong about such harm. This is proven by safety studies of thyroid cancer patients and my own forthcoming study. Yet the endocrinology specialty still tenaciously promotes this false belief. It is high time that Drs. Toft and Hamburger, the British Thyroid Association, the American Association of Clinical Endocrinologists, and other such groups do the decent and humane thing: publicly admit that they have been wrong.

Instead, as I sit here writing, this false belief of the endocrinology specialty is being used to persecute doctors—doctors who know the belief is wrong and who regularly relieve human suffering by violating the dictated guideline based on it. The United Kingdom's Dr. Gordon Skinner is an eminent physician/scientist currently being persecuted. Many patients have told me that Dr. Skinner rescued them after endocrinologists had kept them suffering for years by denying them enough thyroid hormone to get well. On behalf of those patients and others who need rescuing from the specialty's false belief, I ask that endocrinologists like Toft retract their scientifically-refuted belief, apologize for the harm the false belief has caused patients, and cease coercing other doctors to harm their patients through complying with the belief.

This appeal to Toft and his like-minded colleagues is urgent. My assessment is that millions of lives have been ruined by their false belief. And in my opinion, the horrors of terrorism pale when compared to the worldwide harm to humanity done by the endocrinology specialty’s tenacious promotion of this double standard for the treatment of hypothyroid patients.

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by Tammy Lowe

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The Lowe Clinic and Research Center
119 Long Springs Place
The Woodlands, TX 77382 USA
Tel (603) 391-6061 Fax (303) 496-6200 Tammy@drlowe.com

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News Items

- Interview with Helen Foster for the UK Magazine, Psychologies
- Low Blood Sugar Despite a Complex Carb Diet: Finding It and Fixing It

Interview with Helen Foster for UK Magazine, *Psychologies*

On July 19, 2007, I had the pleasure of being interviewed by Helen Foster, a writer for the British women's magazine *Psychologies*. Her article is on hypothyroidism, and I'm only one of the thyroid doctors and researchers she will quote in the article. I am especially pleased to participate, however, because she intends to include information on thyroid hormone resistance. And as many readers of drlowe.com know, few doctors understand anything about this important subject.

I told Helen that not long ago, doctors and researchers thought that thyroid hormone resistance was rare. However, the condition is common, and precious few patients with resistance are treated properly.

I emphasized an important point: one reason that few resistance patients get proper treatment is a dreadful mistake made by conventional endocrinologists—that is, they've defined hypothyroidism as a high TSH level. Patients with the peripheral form of thyroid hormone resistance have "normal" TSH levels. Most endocrinologists let their patients use thyroid hormone therapy *only* when they have high TSH levels. Because of this, most endocrinologists (and other conventional doctors who take their advice) deny resistance patients any thyroid hormone therapy at all.

When my book *The Metabolic Treatment of Fibromyalgia*[1] was published, I included a proposal by Dr. Richard Garrison.[1, pp.322-323] His proposal is that we rename peripheral thyroid hormone resistance "type II hypothyroidism." He was making an analogy to diabetes, in which type I diabetes is a deficiency of insulin, and type II diabetes is insulin resistance. This analogy, as all analogies, breaks down at certain points. However, viewing the need of patients with thyroid hormone resistance from this perspective has humane potential: it could lead doctors to rescue the patients from the conceptual mistake of the endocrinology specialty that no one needs thyroid hormone therapy unless he or she has a high TSH.

Helen made one of her main goals clear to me: She was concerned about how readers of Psychologies can avoid or correct their thyroid hormone resistance. I explained—as I detailed at great length in The Metabolic Treatment of Fibromyalgia[1, pp.226-231]—that man-made chemical contaminants are a major—probably *the* major—cause of thyroid hormone resistance.

Eliminating these contaminants from our bodies (virtually all of us are contaminated with them) is probably the most productive course of action. We should all avoid the foods and other environmental sources of the contaminants. (Successfully avoiding them will, of course, be tough nowadays. The Bush Administration has engaged in a wholesale reversal of environmental protection legislation, and it has given industry free reign to pollute the world with no concern for the adverse impact on human health.) Also, we should occasionally reduce our body fat to liberate the chemicals, which tend to deposit in fatty tissues. Unfortunately, as I said, we're all polluted with these chemicals. Because of this, if environmental pollutants are the major cause of thyroid hormone resistance, it would at best take decades for committed environmentally conscience administrations to free the world of thyroid hormone resistance.

In the interview with Helen, I also mentioned patients with central hypothyroidism. In this condition, the patient has less than optimal thyroid hormone production from a problem with the pituitary gland or hypothalamus in the brain. For many years, I studied the percentage of patients with central as opposed to primary (thyroid gland failure) hypothyroidism among fibromyalgia patients. I found that some 44% of fibromyalgia patients met the criteria, and had "normal" TSH, free T3, and free T4 levels.[2][3] What's important to realize about this finding is that the usual TSH, free T3, and free T4 levels that doctors order *cannot* identify patients who have central hypothyroidism. So, like patients with peripheral thyroid hormone resistance, these hypothyroid patients are forsaken by the endocrinology specialty's poorly-conceived and incredibly limited definition of hypothyroidism. Tragically, most conventional doctors take the specialty's advice as gospel. As a result, they fail to identify these patients and usually deny them the therapy that they so badly need.

Helen and I covered other points, but I'll stop with those I mentioned above. Magazine writers have pressures that dictate what they include in their final articles. Because of this, after one of these interviews, I never know what the writer will use or not use of what I've said. I never know until the final article is published whether I'm quoted at all. I will say, however, that I'm grateful to Helen for anything she includes from our interview. She'll be giving some voice to those of us fighting to liberate hypothyroid patients from the endocrinology specialty's false and harmful beliefs about hypothyroidism. In addition, it was a delight to spend time talking with Helen.

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Low Blood Sugar

Despite a Complex Carb Diet: Finding It and Fixing It

Over the last two years, I've been helping patients to *objectively* identify blood sugar problems through home glucose tolerance tests. Many years ago, I used to order those horrible glucose tolerance tests done at laboratories. I stopped ordering those partly because so many patients were sickened by the large amount of pure glucose the lab personnel required them to swallow. I also stopped ordering them because I don't believe the test results reflect the reality of what happens to a patient's blood sugar after his or her typical meal.

I've had a specific motivation in having patients do home glucose tolerance tests; that is, I wanted to help them identify blood sugar problems that might be interfering with their recovery. I'm happy to say that because of these tests, I've succeeded at helping some patients whom I otherwise would have failed.

I named the clinical approach that I developed in the 1990s metabolic rehabilitation. Most patients who undergo "metabolic rehab" are hypothyroid or partially resistant to thyroid hormone. As probably most of my readers know, the patients' hypothyroidism or resistance has usually been misnamed "fibromyalgia," "chronic fatigue syndrome," or other such mysterious new disease.

To succeed at metabolic rehab, most patients must begin using effective thyroid hormone therapy. For example, when I first see many patients, they are using T4-replacement (in the U.S. and Canada it's usually with Synthroid). Many of these patients soon smoothly recover by switching to more effective therapeutic approaches that include their use of products such as Armour Thyroid or Cytomel. For some patients, though, the path to recovery isn't smooth; obstacles block their way. For them to finally get well, we have to learn what the obstacles are, and then either remove them or get the patients past them in some way.

I began to study the issue of low blood sugar during the time I taught clinical nutrition back in 1979 in the Clinical Sciences Division of the Texas Chiropractic College. Since the early 1990s, I've done my best to persuade patients to go on a diet that corrects low blood sugar.

About two years ago, I decided to start *objectively* verifying the nature of patients' blood sugar problems. As a clinical researcher, objective evidence is, of course, treasure to me. So, I went about collecting evidence in the form of patients' blood sugar measurements. I now have enough evidence to start writing about what I've learned. And I hope that what I've learned will help patients and their doctors improve their treatment results during metabolic rehab.

I've learned a lot in the last two years that has surprised me. For example, I had long held a presumption: that the major blood sugar problem blocking patients’ recovery is *low* blood sugar. However, after many patients sent me the results of their home glucose tolerance tests, I saw that my presumption was wrong. Rather than low blood sugar, most patients’ test results showed the exact opposite—*high* blood sugar. The patients' blood sugar levels weren’t high enough to diagnose diabetes. But their levels *were* high enough to account for symptoms such as fatigue and poor memory and concentration.

Later, I'll write extensively about these patients with high blood sugar. It's important to do so because we now have research-based natural medicine treatments that can help many patients recover from high blood sugar levels. And, these treatments can presumably prevent patients from progressing to frank diabetes.

Here, though, I want to describe a subset of patients I've found who have a blood sugar problem I didn't anticipate. They are patients who generally eat wholesome foods. As part of their various diets, they eat almost exclusively carbs that are complex. They eat foods such as brown rice, whole-grain cereals, hummas, spinach, whole-wheat spaghetti, tomatoes, yams, potatoes, and similar carbohydrate foods. They also eat wholesome protein foods such as lean white meat and healthy-fat foods, such as avocados.

On principle, we usually associate reactive low blood sugar with refined carbs. In contrast, we usually expect people who eat complex carbs to have comparatively normal blood sugar levels. This expectation, however, is wrong for the subset of health-conscious patients to whom I refer!

To illustrate the nature of these patients' blood sugar problem, I'll give the actual test results of a patient whom I'll call Sally. After switching from Synthroid to Armour, Sally improved overall. But she had persisting fatigue and "mental fog." (For clinicians interested in my deductive approach to identifying the causes of persisting symptoms despite otherwise effective metabolic therapy, please see Section IV and Chapter 5.2 of Section V in my book *The Metabolic Treatment of Fibromyalgia*.[1])

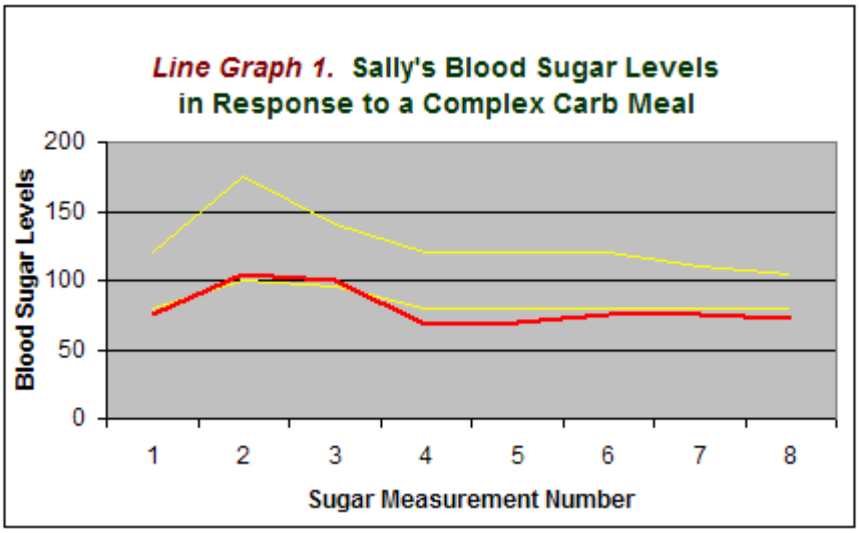
Below, I've provided two of Sally's line graphs. Line Graph 1 shows eight of her blood sugar levels over a six-hour time. I had her measure the blood sugar levels at home before and after a meal of complex carbohydrates. Line Graph 2 shows Sally's cortisol levels at four times over that six-hour time.

Measuring cortisol levels during the glucose tolerance test can help clarify that a patient's blood sugar level drops too low. Assuming that a patient's adrenal cortices (the "cortices" are the outer layers of the two adrenal glands that release cortisol) are working properly, a dip in blood sugar will cause the cortices to secrete more cortisol. As a result, the patient's cortisol level spikes. We can measure this by having the patient take saliva samples at set intervals. (Some doctors with out-dated beliefs say they "don't believe in salivary testing." This attitude is unfortunate; it short-changes patients who could benefit from salivary testing. Hundreds of scientific studies show that the salivary free cortisol is a valid and highly reliable test.)

What Sally's Line Graph 1 shows—as have the graphs of other patients like her—is low blood sugar levels despite a complex carb meal. Her Line Graph 2 shows that her adrenal glands reacted to the low blood sugar by secreting a large amount of cortisol. (I graph the typical patient's blood sugar levels and email the graph to him or her in pdf format. If the patient has also taken salivary samples during the glucose test, I graph those results, too, and email them as a pdf file. That way, when we talk by phone about the results, we can both clearly see his or her sugar levels compared to what lab pathologists consider normal (indicated by the yellow lines in Line Graph 1).

Not all patients' graphs are as clear and telling as Sally's. When they're not, the patient and I must do more diagnostic detective work. Even when a patient's graphs are clear and telling, I often ask the patient to repeat the tests to confirm the sugar and cortisol levels. Sally did a second set of tests, and the results were almost identical to the first.

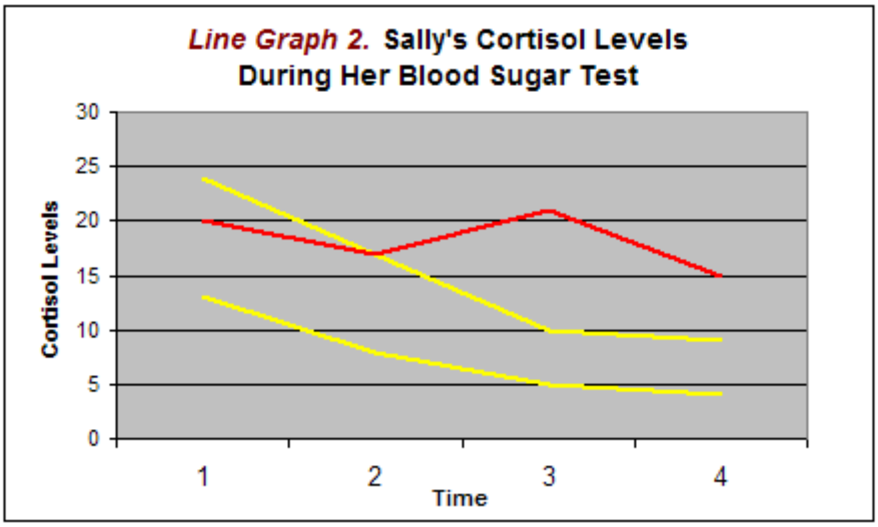
To understand the graphs, keep in mind that the yellow lines in Line Graph 1 mark the upper and lower ends of "normal" blood sugar levels. The yellow lines in Line Graph 2 show the upper and lower ends of "normal" cortisol levels. The red lines in the graphs show what the patient's measured blood sugar and cortisol levels were.



Sample	1	2	3	4	5	6	7	8
Time	Fasting	1/2 Hr	1st Hr	2nd Hr	3rd Hr	4th Hr	5th Hr	6th Hr
Sugar Level*	75	105	100	68	70	76	75	72

*mg/dL

We learned from Sally's cortisol levels that her adrenal cortices were working well (see Line Graph 2 below). They responded as expected to her low blood sugar levels, secreting more cortisol.



Sample	1	2	3	4
Time	Fasting	1 Hr	3 Hr	5 Hr
Cortisol Level	15	12	15	12

Our challenge was to figure out why Sally's blood sugar levels were low. She had eaten about 200 grams of complex carbs. This is enough to raise most people's blood sugar. But her blood sugar levels showed that too little of the sugar from the carbs had entered her blood.

Sally's pattern of low blood sugar and high cortisol, in view of her healthy diet of complex carbs, suggested two possible causes of her low sugar levels. First, as I document in Chapter 3.14 of *The Metabolic Treatment of Fibromyalgia*,[1,pp.681-687] people with too little thyroid hormone regulation typically have impaired digestion and decreased absorption from the small intestine. Sally's hypothyroidism, however, was being treated effectively. Three grains of Armour Thyroid had relieved most of her hypothyroid symptoms and raised her basal temperature and heart rate to normal.

The second possibility was that for some other reason, Sally wasn't digesting and absorbing the complex carbs she ate. I ordered a comprehensive set of intestinal lab tests for her. The results ruled out conditions such as inflammation of her small intestine. However, the test results did indicate that she wasn't secreting normal amounts of pancreatic digestive enzymes, including amylase. (Amylase is a set of enzymes that digest carbohydrates.) This appears to have been the source of Sally’s low blood sugar levels.

Sally began to take a digestive enzyme product that worked for her. It relieved intestinal gas that had been a minor problem. And when she did the home glucose tolerance test twice again, her glucose levels were well within the "normal" range. Most importantly, she was soon free from her mental fog and fatigue.

Sally is representative of several other patients I have worked with over the last couple of years. For them, low blood sugar levels are apparently caused by poor digestion of complex carbohydrates. I'm especially interested in their cases because in the past, I expected only refined carbs to be a source of low blood sugar. Complex carbs are far healthier than refined ones—as long as the patient can digest and absorb them. If not, the proper course isn't to switch to refined carbs. Instead, it is to continue the complex carbs and identify and correct the problem in digesting and absorbing them.

Our Menu of Services: Long-Distance Consulting, Metabolic Evaluations & Treatment

by Tammy Lowe

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The Lowe Clinic and Research Center
19 Long Springs Place
The Woodlands, TX 77382 USA
Tel (603) 391-6061 Fax (303) 496-6200 Tammy@drlowe.com

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- **Thanks to Our Readers and Friends**
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Thanks to Our Readers and Friends

I want to personally thank all of you who have written to express condolences for our loss of our friend and colleague, Richard L. Garrison, MD (http://www.fibromyalgiaresearch.org/aboutfrf/memorial/drrichardgarrison.htm). Your kind and sympathetic words mean the world to all of us at the Fibromyalgia Research Foundation and our Clinic and Research Center. *—Dr. John C. Lowe*

Infertility and Hypothyroidism

On September 6, 2007, I received a question from a woman reader of drlowe.com asking about a common problem: her doctors failing to understanding a relationship she does understand: that between infertility and hypothyroidism.

She and her husband have not, despite their best efforts, been able to get pregnant. The medical literature is abundantly clear about the relationship between infertility and hypothyroidism, and research studies confirm the relationship. Infertility, however, is a common result of untreated or undertreated hypothyroidism. Most fertility doctors, however, appear to exclude this information from their bank of knowledge. They've abandoned proper treatment of hypothyroidism with thyroid hormone. Instead, they virtually always advise couples to use the more recently developed drugs, ones that are still under patent and therefore more profitable to the drug companies that sell them.

This approach of another specialty of modern conventional medicine is emblematic of a major problem of modern conventional medicine. For the most part, the doctors serve as drugs salespersons. Those who suffer as sacrificial lambs are couples who want to normally conceive. It is especially women, however, who may suffer severe adverse effects from the fertility drugs, along with chronic health problems from their untreated or undertreated hypothyroidism.

Right now, there are probably tens of thousands of women who suspect they may be infertile because they are hypothyroid. But their fertility doctors ignore that suspicion and encourage them to use pharmaceutical fertility drugs.

To learn the potential harm of listening to these doctors, I encourage these women and their husbands to go to the following webpage of *PubMed*: http://www.ncbi.nlm.nih.gov/sites/entrez. There, type into the search window the following search terms (without the quotation marks and period): "fertility drugs and adverse effects and review." When I did so this morning, using the qualifier "review," 302 abstracts of review publications came up; when I dropped the qualifier "review" and just requested abstract of published studies, 2158 abstracts came up. If nothing else, read over the review abstracts and consider the cancer risks from ignoring your hypothyroidism and submitting to the use of pharmaceutical fertility drugs.

To me, through the fertility specialty, conventional medicine proffers to us one more horrific scheme of inhumane money grubbing through a commercial venture with drug companies. But alas! Along with some good, such is what conventional medicine generally offers us. What can couples do? Obviously, you can educate yourselves so you can make well-informed, self-protective choices. Not to do so (as the study abstracts I recommend above will show) may mean the ultimate sacrifice by the wife.
Question and Answer on Fertility and Hypothyroidism

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by Tammy Lowe

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The Lowe Clinic and Research Center
19 Long Springs Place
The Woodlands, TX 77382 USA
Tel (603) 391-6061 Fax (303) 496-6200 Tammy@drlowe.com

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- FiMONOCOel is Available
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- Services We Offer

Dr. John C. Lowe

Months ago, we were deluged by email and phone calls from countless thyroid patients in several countries. Many were troubled, and others were terrified, that they were no longer able to purchase Cynomel from offshore pharmacies.

Cynomel had rescued these patients from the misery imposed on them by the endocrinology specialty's cash cow, T4 replacement with levothyroxine. Many of the patients purchased Cynomel from offshore pharmacies and had the benefit of secrete guidance by caring local clinicians. Why "secrete" guidance? Because the clinicians (many of whom I have talked with) are afraid of retaliation from local endocrinologists if the endos learn that the clinician treated a patient with any thyroid hormone therapy than T4 replacement. Never mind that the alternate thyroid hormone therapy enable the patients to recover their health! I know this because I've talked with many of the clinicians. Each one of them has expressed In each case, the message was the same

, and they used it with the guidance of local clinicians. Many other patients, however, had had to resort to treating themselves. They had to if they were to get effective thyroid hormone therapy. Local clinicians were too intimidated by the endocrinology specialty to prescribe any synthetic T3 product, despite the fact that the specialty's cash cow, T4 replacement, left many of the patients miserable, and others outright disabled.

New Thyroid Hormone Product as Effective as Cynomel

(***Update:*** April 8, 2009:
The new product, Hypo Support Formula,
is now available to patients and clinicians.)

In August and September of 2008, patients began contacting us expressing frustration at no longer being able to obtain Cynomel, the quality T3 product produced by Grossman in Mexico. They were running out of their supply, and, naturally, they were frustrated and frightened. They had improved or recovered with Cynomel after having suffered from being restricted to treatment with T4 products. No access for them to Cynomel forebode recurring symptoms.

We immediately began to look for an effective alternative to Cynomel and we found a promising one. To make sure it was effective, and to learn how it compares to Cynomel, I designed a study. The study took three months and we've now completed it. We can't yet disclose the name of the product or its source, but we should be able to within weeks.

The product is organic; it's the only organic thyroid hormone product I've ever heard of. The company that markets it has taken extraordinary steps to make sure it is, as one company official said, *pristinely* organic. In years past, many organic farms where animals are raised used man-made chemicals. Residue from these chemicals may still be in the soil and grass. If they are present, the residual chemicals may still contaminate to some degree the animals on the farm. The product we've tested, however, comes from a source that completely sidesteps possible residual contamination.

In the study we've just finished, we learned that the product is as effective as Cynomel. In fact, we found that it provided some benefits beyond those from Cynomel. We also found the product's clinical equivalence to Cynomel. This means that we now have information for clinicians and patients on the proper use of the product.

We are already well into a second study intended to affirm the clinical equivalence of the product to Cynomel. Also, a number of patients are using the product as part of an on-going clinical trial. *Thyroid Science* (www.ThyroidScience.com) will publish reports of these studies when they are done. The report of the first study will appear in *Thyroid Science* within the next two weeks. When it's published, we'll email a notice that the paper is available (free of charge) online. We'll also be providing detailed information about the product within the next couple of months.

(***Update:*** April 8, 2009: The new product, Hypo Support Formula,
is now available to patients and clinicians.)

Electronic and Geratherm Thermometers:
Both Give Consistent Readings

A few weeks ago, we finished a study in which we compared inexpensive electronic thermometers (digital readouts) to Geratherm thermometers. Geratherm thermometers have replaced mercury thermometers, which are no longer sold.

Researchers have compared both electronic and Geratherm thermometers to mercury thermometers. But to my knowledge, no one before has compared electronic thermometers to Geratherm thermometers. I conducted a study in which I compared them statistically.

I did the study partly because some clinicians contend that the readings from electronic thermometers vary too much. They didn't, however, in this systematic study. The readings from the two types of thermometers tightly correlated. For all practical purposes, both types gave consistent enough readings for clinical use.

A value of electronic thermometers is that they give readings faster. A value of “Geratherm Hypothyroid Thermometers,” the type we tested, is that the measurement units are spread far enough apart so that it’s easy to see small gradations in temperature.

Thyroid Science's journal staff will send an email to let readers know when it publishes the study. You can, of course, always check the latest publications of the journal by going to the homepage, www.ThyroidScience.com, and clicking on "Editorials and Latest Postings."

Dr. Lowe's Services

Tammy Lowe

If you want to discuss the services we provide, please contact me. You can reach me by email at Tammy@drlowe.com, or by phone at 603-391-6061.

Dr. John C. Lowe, PLLC
19 Long Springs Place
The Woodlands, TX 77382 USA
Tel (603) 391-6061 Fax (303) 496-6200 Tammy@drlowe.com

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Archived Newsletters

Please Note: I've revised the original version of the article below. The main change I made is this: I switched my recommendation for the dietary desiccated thyroid product of choice from RLC Labs' Hypo Support Formula (HSF) to Thyro-Gold™. I did this for a specific reason: In good conscience, I can no longer recommend HSF. I can't because of what I believe to be problems with the product. My belief is based on three things: two years of studying HSF, telling communications with credible sources, and the published history of the use of what we now call "dietary desiccated thyroid." I learned of problems with HSF only gradually. For a time, while Thyro-Gold™ was being developed, HSF was indeed the product of choice. However, in my opinion, it no longer is. As my wife Tammy said to me this morning, "Good science means positive change." And I believe that the scientific investigations we've conducted over the last two years have brought about a very positive change. That change is the availability of what I believe to be the best choice among dietary desiccated thyroid products, Thyro-Gold™ and Thyro-Gold™ *Plus*. *—Dr. John C. Lowe, LLC (May 3, 2010)*

No More Begging and Pleading with Misguided Doctors: Liberation through Self-education, and Action on Your Own Behalf

Dr. John C. Lowe
May 8, 2009

I received the question below at AskDrLowe@drlowe.com yesterday. Since I wrote my answer to the woman's questions, I've had to control the outrage that I must quash inside myself every day. It wells up from my awareness of the misery hypothyroid patients suffer from the commercially-driven dictates of the endocrinology specialty (dictates that the specialty euphemistically calls "practice guidelines").

At the same time, I've felt a mixture of other emotions from my memory of conversations with many practicing clinicians. They've admitted to me that they know the specialty's dictates harm patients. They comply with the dictates, however, from fear of retaliation from the endocrinology specialty through medical regulatory boards.

I feel especially outraged over the suffering of British patients from the recent diagnostic and treatment recommendations of the British

Thyroid Association and the Royal College of Physicians. I say "especially outraged" because I fully expect that the recommendations will cause even more widespread suffering than already afflicts so many British hypothyroid patients.

As I reflect back over my years of clinical practice, I see countless faces of hypothyroid patients. Most of the patients had long suffered due to the endocrinology specialty's dictates. Many of their faces were wet with tears, others were clinched tight from anger, and still others were weary or despondent from the dismal days-and-nights the dictates had caused them to suffer through. And I can never stop thinking about all the people yet to become hypothyroid, many of whose lives those dictates will spoil, outright ruin, or bring to a premature end.

I know some clinicians who courageously violate the specialty's dictates. By doing so, they get many hypothyroid patients well. But those few clinicians practice medicine in constant danger of local endocrinologists filing complaints against them with medical regulatory boards. The complaints most often cite the clinicians for suppressing patients' TSH levels. Only if a hypothyroid patient has had thyroid cancer does the endocrinology specialty approve suppressing his or her TSH, allowing the benefits that come from it, such as a longer life, improved health, and an improved sense of well-being.

But if a patient hasn't had cancer and suppresses his or her TSH with thyroid hormone, the increased life span, better health, and improved well-being, according to the specialty, *must* be "placebo effects." And the specialty warns that the price the patient is likely to pay for enjoying those "placebo effects" is osteoporosis, adrenal crisis, or sudden death from a heart attack. No endocrinologist I've ever asked has explained to me why these adverse effects don't befall thyroid cancer patients who live for decades with suppressed TSH levels. But feeling justified in "protecting" the non-cancer patients from their TSH-suppressing clinicians, some endocrinologists send complaints to regulatory boards, and woe betide the cited clinicians.

For hypothyroid patients and their TSH-suppressing clinicians, the circumstance involving the endocrinology specialty isn't improving but is getting worse. Because of that, I've come to believe that a particular route is best for many of these patients to take. If they don't have collaborative, dictate-violating clinicians to help them get well, the next best route to follow—rather than allowing the dictates to keep them sick—is to turn away from conventional medicine and educate and treat themselves.

Fortunately, in the U.S., hypothyroid patients are at liberty to do this, at least for the time being. They can do it thanks to the 1994 Dietary Supplement Health and Education Act. That Act allows access by personal choice to effective medications classified as "dietary supplements" rather than FDA-regulated drugs. Patients don't need prescriptions to use dietary supplements; all they need is the knowledge of how to properly use them and the gumption to turn away from Big Pharma's drugs and put the dietary supplements to use.

For anyone who benefits from the information I include here, I ask only one thing in return: that you be ever vigilant for what, at the root, are Big Pharma-prompted attacks on the 1994 Act. And when those intermittently-occurring attacks are under way, take prompt action by letting your legislators know that you demand the health freedoms the Act ensures. (You can learn of these attacks and conveniently let your legislators know you oppose them by subscribing to two newsletters by natural health activist groups: Alliance for Natural Health and Citizens for Health.) When we can, we'll let you know at drlowe.com when the Act is under attack, and we'll be grateful for your steadfast and repeated defense of it along with ours.

Now . . . here's the email inquiry I mentioned at the start that set off all these thoughts, and my response to the person's questions.

Question: I have Hashimoto's and was feeling like a new human being on 2 grains of a prescription desiccated thyroid product. I'd *never* felt as good before in my life. Then, last month I went in for my regular visit to my family doctor and she checked my thyroid. Her nurse called a week later and said my TSH was too low and I was overstimulated. She made me drop my dose from 2 grains to 1. I did, and for the last week, I've felt like a slug again. I'm depressed and constipated, and I'm freezing and wearing a sweater while everybody else is in T-shirts, bare feet, and flip-flops. I called and told the nurse that I had felt great on 2 grains and that I did not feel overstimulated at all. I also told her how awful I've felt since dropping my dose to 1 grain. She put me on hold, and when she came back, I was shocked at what she said. She told me the doctor said I'm better off feeling awful than getting bone fractures or a heart attack from too much thyroid. Are those really my only two choices, feeling awful or dying from a heart attack? Do I have to beg and plead to use enough thyroid hormone to feel well, like I did on 2 grains of the prescription desiccated thyroid product?

Dr. Lowe: I'm sorry your doctor sent you on a toboggan slide to suffering again. She apparently has been effectively propagandized by the endocrinology specialty, whose beliefs about the TSH, I staunchly believe, are purposely shaped by boardroom executives of corporations that own TSH test kits and sell them by the millions to laboratories for clinicians to order.

The scientific evidence shows that even if you have a suppressed TSH, with a high degree of probability, that won't cause you to develop osteoporosis. In fact, if the 2 grains of the prescription desiccated thyroid product enabled you to be more active, you may have bone density that's higher than that of other women your age.

Your doctor seems to have been misled to a false belief: that she can accurately deduce from your TSH level what your bone density is. Of course, that's nonsense. She can find out exactly what your bone density is by ordering the test called "bone densitometry"; but *never* will she know what your bone density is from the level of your TSH.

And a heart attack from 2 grains of desiccated thyroid? Your doctor, in my opinion, should be ashamed of herself; she couldn't subscribe to that belief if she is were half-rational and had read the relevant research reports in the medical literature. That statement alone shows that she's either under-educated or uneducated about a therapy she's prescribing; to me, that's professionally irresponsible. As she should know, you're far more likely to have a heart attack from *too little* thyroid hormone than you are from *too much*. Proper testing is readily available so that she can accurately find out what your heart status is, and that testing does *not* include your TSH level.

Fortunately, you and others don't have to put up anymore with doctors making you suffer from hypothyroid symptoms. And you no longer have to put up with her or any other doctor causing you to develop coronary artery disease or low bone density by forcing you to take too little thyroid hormone. Prescription desiccated thyroid products are usually effective. But they are effective *only* if your doctor lets you use enough of it to get well.

But with a doctor as misguided as yours, and who restricts you to too low a dosage, you can simply switch to Thyro-Gold™. This product is classified as a dietary supplement, and because of that, using it doesn't require a prescription. I found in two clinical trials so far (trials with Thyro-Gold™ are under way) that dietary desiccated thyroid, when it's used properly, can be as effective as any other thyroid hormone product. It would be best if you had a doctor well-educated about hypothyroidism who'd work with you in using Thyro-Gold™. But if not, you can use it as you see fit, free from any doctor interfering with your self-treatment through his or her false beliefs about TSH levels. We will be closely monitoring scores of patients who use Thyro-Gold™. People we've monitored who've properly used dietary desiccated thyroid and found their individual optimal doses (with total disregard for their TSH levels) have said they felt extremely well—just as you say you felt on 2 grains of the prescription desiccated thyroid product.

If you use Thyro-Gold™, I believe you can best avoid interference from your doctor by you refusing to let him orher order another TSH test. If the doctor asks about your thyroid status, you can tell him or her not to bother over it. You can also say that your thyroid condition is being taken care of by someone who knows best how to handle it. That person, of course, is a well-informed *you*.

You being "well-informed," of course, means knowing how best to handle your own hypothyroidism. I encourage you—as I do every patient forsaken by his or her doctor's ignorance of clinical thyroidology—to read, read, read, and learn *everything* you can about hypothyroidism and how to properly treat yourself for it. (A good place to start is drlowe.com. At drlowe.com, we have close to 400 pages of information free of charge. I also strongly recommend my encyclopedic coverage of hypothyroidism, thyroid hormone resistance, and fibromyalgia (which only one set of symptoms from too little thyroid hormone regulation), and their proper treatment. That coverage is in my book *The Metabolic Treatment of Fibromyalgia*.)

Properly treating yourself for hypothyroidism is basically this: treating yourself as most doctors treated hypothyroid patients before the mid-1970s. After that time, the endocrinology specialty came more-and-more to promote the use of the TSH, as corporations made vast fortunes off the test and shared the profits with the specialty. Nowadays, when it comes to diagnosing and treating hypothyroidism, an implicit motto indelibly stains the collective brain of the endocrinology specialty. That motto is, "The TSH and the TSH alone in the service of health . . . and, as a side benefit, power and profit!" The specialty imposes this motto on other clinicians through its "practice guidelines," which are actually dictates imposed on clinicians and their patients at the expense of the health and well-being of millions of hypothyroid patients. But you don't have to let this institutional falsehood (that the TSH is the test of choice) harm you any longer.

Concerning your self-education about hypothyroidism, I can tell you one thing with confidence: You won't have to read much before you know more than most doctors do about the disorder. And I believe those doctors whose knowledge you'll surpass include most members of the endocrinology specialty. Because most doctors have little knowledge of hypothyroidism, and because they're likely to try to impose the specialty's dictates on you, it's important that you also learn to *resolutely* tell these doctors that you don't care for their opinions on your thyroid status and your thyroid treatment.

As I final thought, I think you can feel good about a fortuitous turn of events for hypothyroid patients such as yourself. And that turn of events is my answer to your last question: *Never again do you have to humble yourself before some misguided doctor and beg and plead to take enough thyroid hormone to enjoy good healthy.*

I've included below links to three chapters from a book I wrote. In the chapters, I explain how most people, such as you, can safely get well with thyroid hormone. I've given you links to the chapters because of a firm belief I hold. That belief concerns what I see as the best way for hypothyroid patients across our globe to escape the wide-scale harm to health caused by the endocrinology specialty's dictates. That way from harm to health is this: *liberation through self-education, followed by well-informed action on one's own behalf*. You're free to share the chapters with anyone else who wants the basics for escaping illness-sustaining medical care and beginning their short journey to recover from hypothyroid symptoms. My sincere best wishes to you for soon feeling healthy again.

Free Book Chapters for Self-treating Hypothyroid Patients

| Metabolic Rehabilitation | Numbers Count |
| Safely Getting Well with Thyroid Hormone |

A gift to you with my best wishes
for you soon safely getting well,
Dr. John C. Lowe

Our Services

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Dr. John C. Lowe, PLLC
19 Long Springs Place
The Woodlands, TX 77382 USA
Tel (603) 391-6061 Fax (303) 496-6200 Tammy@drlowe.com

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Is it Irresponsible to Advise Hypothyroid Patients to Treat Themselves with HSF? One Physician Thinks So

Dr. John C. Lowe

Our last email newsletter, titled "No more begging and pleading with misguided doctors," brought a deluge of emails to Tammy and me. All but a couple are extremely positive. Most of the emails were from patients, but several were from physicians and other health care practitioners.

All but one of the emails from physicians contain expressions of agreement, thanks, or support. All but the one below. In his email, this physician opines that my advice to hypothyroid patients to treat themselves is irresponsible.

I ask that in reading my reply to this doctor, physicians who consider themselves "conventional" bear something in mind: I believe that most conventional physicians conscientiously try to avoid harming their patients. But their efforts, as many studies show, are too often thwarted. This doesn't mean that the physicians are malicious toward their patients. Instead, it means that they work within a bad system—a system corrupted by large corporations' financial and other inducements to many high-profile, influential decision-makers who dictate how conventional physicians must practice, if they are to keep their medical licenses. Many conventional physicians I've talked with are fully and painfully aware of this. For this very reason, thousands of them are jumping off the ship of conventional medicine onto the deck of natural, alternative, complimentary medicine, or whatever one wishes to call it. Those of us on that less-corrupted and *safer* ship welcome the jumping doctors with open arms.

May 12, 2009
Comment: I'm a physician, and I think you're advice to patients to make their own treatment decisions and treat themselves for hypothyroidism borders on a violation of ethics. MDs are the only ones educated to decide what medications patients should take. Patients don't have medical educations and they aren't qualified to make medical decisions. By advising them to treat themselves, you're putting them at risk of harming themselves, and I think that is irresponsible of you.

Dr. Lowe: Thank you for your opinion, to which I will reply. But before getting to your main point, I want to deal with one you've perhaps inadvertently implied.

You seem to think that I've encouraged patients not to work with clinicians at all. If so, you're wrong. I've made it clear elsewhere that it's best for each patient to work with a local clinician—but *only* if the clinician is truly knowledgeable about, and effective at treating hypothyroid patients. However, if a physicians rigidly complies with the dictates of the endocrinology specialty and denies hypothyroid patients any thyroid hormone treatment other than T4 replacement, then I believe that physician will fail to effectively treat *far* too many hypothyroid patients.

To effectively treat most patients, physicians have to violate the endocrinology specialty's commercially-derived practice dictates. But violating those dictates may cause the physician to lose his or her license to practice clinically—with the endocrinologist who files a complaint against him or her and the regulatory board that prosecutes him or her totally ignoring the physician's effectiveness in treating hypothyroid patients. This unfortunately limits the number of physicians available to effectively treat hypothyroid patients.

The Problem in Finding a Physician Who is Effective at Treating Hypothyroidism

What I've just described is to me a bizarre circumstance; at the same time, it's a categorically real one. Many physicians get hypothyroid patients well with thyroid hormone therapies other than T4 replacement after T4 replacement failed to do so. But these physicians must keep a low profile if they're going to keep their license to practice medicine. Otherwise local endocrinologists are likely to file complaints against them with medical regulatory boards. The physicians are then likely to find themselves spending their kids' college funds and their retirement savings fighting the medical board.

The intimidation of physicians by endocrinologists filing complaints leads to many physicians practicing "underground," so to speak. That makes them hard for hypothyroid patients to find and work with. And, of course, if a complaint has led to a physician's medical license being suspended or revoked, patients are then deprived of his or her effective care altogether.

So what are the hypothyroid patient's other choices? One is to settle for the endocrinology specialty's practice dictates. Of course, that's means he also settles for the dreadful state of health that the dictates ensure for many hypothyroid patients.

Another choice is for the patient to take matters into his or her own hands. That entails at least two steps: (1) learning everything possible about hypothyroidism, including how to safely and effectively treat it; and (2) obtaining a high-quality dietary desiccated thyroid product, such as Thyro-Gold™, and using it to recover good health.

Should Conventional MDs Control Access to Dietary Desiccated Thyroid?

You, of course, strongly object to patients taking this second option. You appear to think patients are incapable of treating themselves *safely*. And you imply that only physicians ensure patient safety. That belief, however, is more than highly debatable. Let me explain why I say this.

Like you, several other MDs have grumbled to me: "Some of these dietary supplements [such as Thyro-Gold™] are as powerful as prescription drugs. Patients should have to get a prescription from a physician before they're allowed to use these supplements; *any* supplements for that matter. Patients don't know how to keep from hurting themselves. And because of that, some of them are going to kill themselves messing around with dietary supplements."

I ask you to consider the safety track record of your conventional medical colleagues. After considering what I present below, tell me whether you think it's rational for patients to trust conventional physicians to safely guide them through *any* type of medicinal treatment, whether it's with dietary supplements or prescription drugs.

Consider a 1999 report from India.[1] For every 100 patients who were admitted to hospitals, up to 7% had adverse drug reactions. (That was 7 patients out of a 100, 70 out of 1000, and 700 of 10,000.) Drug-related problems caused three problems: failed therapy (23%), patients developing medical problems they didn't bring to the hospital (10%), and damage that could lead to *"serious permanent disability or death" (42%).* Please pay particular attention to this finding: *Medical negligence was involved in 34% of adverse drug events, and negligence was involved in 51% of drug deaths*. [Italics mine.]

In the US state of New Jersey, a study showed that between 1977 and 1988, medical errors resulted in malpractice suits in which $30,144,636 was paid out.[2] The researchers wrote: "A review of these files revealed that *patients incurred death and serious morbidity*, and that several specific behavior errors accounted for the majority of patient injury." (Italics mine.)

The researchers also wrote, "Among the damages that occurred during that time period were *88 deaths*, 15 patients with *profound brain damage*, 15 patients who alleged that they *had become addicted to medications* prescribed for pain, 10 patients who required *amputations of limbs*, and 12 patients who suffered some degree of *hearing loss or decreased visual acuity*." (Italics mine.) Here are the medical screw ups that injured and killed patients: "disregarding patient allergies," "failing to monitor therapy," and "errors in the writing of prescriptions."[2]

A Nobel Prize winning Harvard physician tells us that mainstream medicine *fails to help 75% of its patients*.[3] But far worse than just not helping patients is another study finding: that is, *the medical system—run by conventional MDs—causes the unnecessary deaths of 224,000 US citizens* *each year*.[4][5]

I could go on-and-on citing studies that show that conventional MDs *dreadfully* harm the public, partly through their control over prescription drugs. But should all the evidence of harm done by conventional MDs inspire hope in us for positive change in their performance? Not according to my old mentor, Robert S. Mendelsohn, MD, a thirty-year medical professor at Loma Linda University School of Medicine. He said that modern medicine doesn't learn from its mistakes, no matter how well-documented they are. Instead, he said, "In modern medicine, the changes that are made are like lateral passes in football: lots of razzle-dazzle, but no yardage gained." Modern medicine just goes on helping maybe 25% of its patients[3] while it maims and kills others.

Despite conventional MDs' abysmally bad safety record, you suggest that they should control who can and can't use dietary supplements. And I trust that you think they should dictate exactly how patients use the supplements. You're recommending that conventional MDs have totalitarian control over *all* health decisions involving medicines and dietary supplements. Realistically, Big Pharma might eventually pull political strings that impose your advice on US citizens, and I think that should scare the hell out of every health-conscious person in the United States.

Considering the evidence, do you *seriously* believe that the track record of conventional MDs warrants putting them in control of effective dietary supplements? I don't believe that hypothyroid patients who treat themselves are likely to cause themselves any noteworthy harm; after all, they have their own best interests at heart. Because of that, it's doubtful that they'll do even a small fraction of the harm done to them over the last forty years by the endocrinology specialty's practice dictates.

Please keep in mind that Thyro-Gold^{TM}, like scores of other health care products, is protected by the Dietary Supplement Health and Education Act. Congress wisely passed that Act in 1994. It did so at the urging of public interest groups, many physicians, and eminent scientists such as Professor Linus Pauling. And fortunately for the public welfare, Congress passed the Act despite vigorous protests from conventional physicians and corporations that richly fund medical specialties. As a result of that 1994 Act, your medical education, degree, and license give you no control whatsoever over patients choosing to use products protected by the Act. Among those products is Thyro-Gold^{TM}, a dietary supplement that's highly likely to improve the lives of countless patients who formerly suffered from the endocrinology specialty's dictates for the diagnosis and treatment of hypothyroidism.

All that said, doctor, I appreciate you expressing your opinion, and I remain respectfully open to an evidence-based rebuttal from you.

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Starfield is with the Department of Health Policy and Management, Johns Hopkins School of Hygiene and Public Health, 624 N Broadway, Room 452, Baltimore, MD 21205-1996, USA.)

Once again, Tammy and I included below links to three chapters from a book I wrote. In the chapters, I explain how most people, such as you, can safely get well with thyroid hormone. We believe that the best way for the incalculable numbers of people suffering from the dictates of the endocrinology specialty (it's "practice guidelines" for the diagnosis and treatment of hypothyroidism) is liberation through self-education, followed by well-informed action on one's own behalf. Feel free to share the chapters with anyone else who wants to learn the basics for recovering from hypothyroid symptoms.

Free Book Chapters for Self-treating Hypothyroid Patients

| Metabolic Rehabilitation | Numbers Count |
| Safely Getting Well with Thyroid Hormone |

A gift to you with my best wishes
for you soon safely getting well,
Dr. John C. Lowe

Our Services

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Dr. John C. Lowe, PLLC
19 Long Springs Place
The Woodlands, TX 77382 USA
Tel (603) 391-6061 Fax (303) 496-6200 Tammy@drlowe.com

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drlowe.com/contactus.htm (603) 391-6061 Tammy@drlowe.com

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Forsaken People: My Main Motive for Thyro-Gold^{TM}

Having seen so many forsaken thyroid patients through my years of clinical practice, I know that pensive look of inner suffering. It says to me that this person instinctively *knows* she's taking too little thyroid hormone. But, then, she's confused and troubled.

Of my thirty-one years of clinical practice, I spent some twenty-five years working with hypothyroid and thyroid hormone resistance patients. During that time, countless patients, on their first visit, had a look on their faces that I'll never forget. It was a pensive look of inner suffering. The look on the woman's face in the black-and-white photograph to the left is what I'm referring to.

Many of these patients later told me that upon meeting me, they'd feared I was just one more clinician who would tell them what they'd heard before. Doctors had told them: (1) You may feel well on the higher dose of thyroid hormone, but that dose has lowered your TSH levels "below-range"; (2) having a TSH level "in-range" is what's important, not how you feel; and (3) if you stay on the higher dose, you risk having osteoporosis and a heart attack.

Patients who had that look taught me what it says: that this person instinctively knows she's taking *too little* thyroid hormone, not too much. But she's confused and troubled. Her doctor, whom she generally trusts, reassures her that her current low dose of thyroid hormone is exactly right for her, as her in-range TSH levels prove? She knows the doctor is sincere when he's warns her that a higher dose is a serious risk. But the only time she's felt close to normal is when she mistakenly took twice the dose he prescribed. Should she trust him and his medical education? Or should she trust her own instincts?

Through the years that I worked clinically with these patients, hundreds of them recovered their health, became more functional, and ceased to show a forlorn face. All my team did to accomplish this was to let the patients do what they instinctively felt they should do—ignore their TSH levels, switch from T4 alone to T3 or a T3/T4 combination product, and find a non-overstimulating dose that enabled them to feel normal again.

Self-treating People. This past week, a frustrated and despondent woman consulted me long distance. She told me about her interaction the week before with her long-time primary doctor. She'd told him, "I was so desperately ill last month," Dr. Mason, "that I increased my Thyrolar [synthetic T4/T3 combination] dose. You've had me on half a grain for better than a year now, and I just felt horrible. I hope it doesn't upset you, but I increased my dose to a grain and a half. For two weeks now, I've felt closer to normal than I have in years."

"But look here," he responded, pointing to her lab report. "You've suppressed your TSH. You *must* drop your dose back down right away."

She pleaded with him. "If you'll let me stay on the one and a half grains, I'll sign a waiver and have it notarized. I'll say in the waiver that I take full responsibility for any problems the grain and a half cause."

The doctor declined, commenting, "That would be bad medicine." Out of frustration, she retorted, "Is it not bad medicine keeping my dose so low that I'm sick and can hardly function?" With this, she'd passed the line. On the spot, he terminated their doctor/patient relationship. He asked her to find another primary doctor. After a week of tortured debating with

Thyro-Gold^{TM} and Thyro-Gold^{TM} *Plus*

Contains Thyroid Powder from Pasture-Fed New Zealand Cows

In our April 17th newsletter, I wrote that the thyroid powder in Franconia's new dietary desiccated thyroid product Thyro-Gold^{TM} would contain Argentine beef. However, this first time around in the production of Thyro-Gold^{TM}, we've instead used powder from pasture-fed New Zealand beef.

We have an excellent source of thyroid powder in Argentina, but using that source would have required Franconia to delay for a month production of the first round of Thyro-Gold^{TM}. Happily, though, customers can now order the product: http://www.thyroidscience.us/products/thyro.gold/intro.thyro.gold.htm.

Franconia's source of thyroid powder in New Zealand is equal to the high quality of the Argentine thyroid powder. New Zealand is among the countries that has banned Monsanto's genetically modified hormone POSILAC, which the pharmaceutical giant Eli Lilly acquired in August 2008.[1] POSILAC is a genetically modified hormone called "recombinant somatotropin," or "rBST." The hormone is used in the beef industry to stimulate calves to grow and adult cows to produce more milk.

In June 2007, the World Organisation for Animal Health granted New Zealand the status of "negligible risk" of mad cow disease.[2] "Negligible risk" means that the risk is so small, trifling, and unimportant that we can safely disregard it. This is the World Organisation's most favorable status, a ranking shared by Argentina, Australia, Uruguay, and Singapore. In contrast, the U.S., Canada, Chile, Brazil, Switzerland, and Taipei China have "controlled risk status." This risk status places restrictions on the U.S. in trading beef products with other countries. The restrictions don't apply to New Zealand and Argentina.

New Zealand has never had a report or record of mad cow disease. And like Argentina, New Zealand is free from other similar diseases, called "transmissible spongiform encephalopathies." The European Commission, for example, recognizes New Zealand as free from the spongiform encephalopathy named "scrapie."[3] Scarpie is an infectious brain disease of sheep that's usually fatal.

Thyro-Gold^{TM}, then, is clean and disease-free, and Franconia Ltd ensures that this will *always* be the case. In addition, Thyro-Gold^{TM} is free from what I believe are problems with Hypo Support Formula (HSF). With those assurances, my research team and I can continue our studies of Thyro-Gold^{TM}, which we've already begun. We'll publish the studies as soon as we have the results so that customers know what we learn about the safe use and benefits of the product.

If you use Thyro-Gold^{TM}, we'll be grateful if you'll share your impressions with us. We'll carefully consider what you tell us, and we'll use your impressions and the results of our systematic herself, she decide to learn how to take charge of her own care. Having read articles I've written on self-care (see below), she consulted me to begin learning how.

In my last ten years of clinical practice and in the subsequent two, I've met many people such as this frustrated and depressed woman. Many of them, by taking control of their own health care, have recovered good health. Many have done so by using dietary desiccated thyroid. With these products, which don't require a prescription, they've had the liberty to take as much as they've needed to finally feel well again. My communications with these people have taught me something important: that many thyroid patients can learn what they need to know to safely get themselves well.

I must say, however, that having a cooperative and collaborative clinician can be a noteworthy help. But if the only clinicians available are of the T4-replacement state of mind, I believe patients can do best by rejecting that poor therapeutic option and taking charge of their own care. If you feel this way, I have a few recommendations:

- First, read the three newsletter articles I wrote in 2009 on self-treating patients:
  - No More Begging and Pleading with Misguided Doctors
  - How-to Information for Self-treating Hypothyroid Patients
  - Is it Irresponsible to Advise Hypothyroid Patients to Treat Themselves?
- Second, download the three free chapters from a book I wrote, *Your Guide to Metabolic Health*. In these chapters, I go over the basics for proper self-guided thyroid care.
- Third, read the Q&As at ThyroidScience.us about safe and effective self-care.

Finding a Clinician Who Can *Really* Help. Many people, of course, are more comfortable with the help of a clinician, and, as I said, I encourage people to do so, if they can find one who'll help and not interfere. If you're among these people, today you have good alternatives to clinicians whose mistaken beliefs or fear offer only T4 replacement.

Naturopathic physicians are a superb option. They prescribe in some states in the U.S. In states where they don't prescribe, they can guide patients in the proper use of dietary desiccated thyroid, such as Thyro-Gold$^{\text{TM}}$. So can a small percentage of chiropractic physicians, those who focus in their clinical practices is on nutrition and general problems of health. Most people don't know, but some chiropractic physicians are board certified in internal disorders and diagnosis. I strongly recommending finding one of these who is knowledgeable and experienced in the treatment of thyroid disorders.

You may know that if MDs and DOs gain much attention from getting thyroid patients well with alternatives to T4 replacement, a local endocrinologist may file a complaint against the physician with the medical regulatory board. This enforcement system understandably intimidates many MDs and DOs from treating patients effectively with thyroid hormone.

A solution to this problem of intimidation is developing. If you know an MD or DO who wants a way past this shameful obstacle to effective thyroid treatment, recommend that he or she become involved in the anti-aging specialty. Some physicians have told me that their anti-aging organization has its own guidelines for the diagnosis and treatment of hypothyroidism. They've said that within the anti-aging specialty, these guidelines supersede those of the endocrinology specialty. Unlike the guidelines of the endocrinology specialty, those of the anti-aging specialty are scientifically rather than commercially based. As a result, anti-aging specialists are helping rescue many victims of T4 replacement, and you may be able to find one to work with.

Summing Up. Regardless of the type of practitioner you prefer to work with to recover your health, you *do* have options nowadays. One of my main aims for the rest of my days is to help as many people I can to understand those options and how to safely use them to achieve optimal health. My most sincere hope is that by working to achieve this objective, I'll get word to enough people so that we'll all see *far* fewer people who silently suffer and show it through that forlorn expression on the faces.

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studies to improve the product in any way we can.

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Please Take Part in Protecting Our Rights to Natural Health Methods

Big Pharma and some legislators don't want us to have natural health options, such as dietary supplements. The legislators frequently try to slip legislation past that would deprive us of those options. A recent case in point is Senator Waxman sneakily inserting an anti-supplement bill deep within the recent financial reform bill. Only the diligent scanning of natural health advocates brought his bill to light. You can learn of these attacks on our freedoms and conveniently let your legislators know you oppose them. You can do so by subscribing to one or both of two newsletters by natural health activist groups: Alliance for Natural Health and Citizens for Health. *Thank you for taking part.*

Our Educational Consulting Services

Tammy Lowe

If you want to discuss the educational consulting service we provide for patients and clinicians, please contact me. You can reach me by email at Tammy@drlowe.com or by phone at 603-391-6061. Our fax number is 303-496-6200.

Podcasts of Janie Bowthorpe Interviewing Dr. Lowe Available

Janie Bowthorpe of Stop-the-Thyroid-Madness interviewed Dr. John C. Lowe on January 7 and January 14, 2010. Janie provides recordings of the interviews. You can either listen or download the recordings. The recordings are available at the following website: http://www.talkshoe.com/talkshoe/web/talkCast.jsp?masterId=62603&cmd=tc

When you reach the page, look for "Episode 8" (1 hour 36 minutes) and "Episode 9" (2 hours 7 minutes). To download the recordings, click on the download buttons; to listen to them, click on the listen buttons.

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Newsletter

June 24, 2010

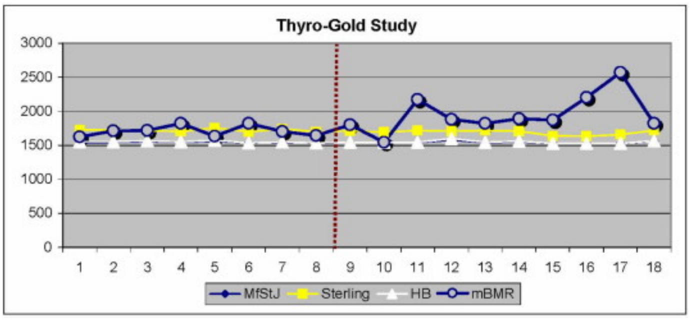
Thyro-Gold More Potent than Expected

Dr. John C. Lowe
drlowe.com ThyroidScience.com

Dear Friends,

It is unusual to report the outcome of a study before the official journal paper is published. However, we have information that we believe is extremely important to those who use Thyro-Gold or dispense it to their patients.

The information is that the product has a potency higher than we expected. We initially heard this from people who have used Thyro-Gold, and now we have confirmed it in two initial formal studies. The two studies will soon be published, but we believe the information is important enough to send out this letter beforehand.



To make sure that Thyro-Gold is of the highest quality, the manufacturer obtained the raw thyroid tissue from New Zealand. You may have noticed that most companies that market dietary desiccated thyroid products no longer report New Zealand as the source of their raw material. From what I've learned by being involved in all stages of making Thyro-Gold available for customers, I've learned that most companies have moved to countries other than New Zealand for their raw material. The reason appears to be the relatively high cost of obtaining New Zealand thyroid tissue. Franconia Ltd, however, didn't let that be an obstacle to including New Zealand bovine thyroid tissue in Thyro-Gold.

Initial Studies of Thyro-Gold. As soon as Thyro-Gold was available, we promptly began the studies of the product that we had planned. This initial research has involved a type of study called a "dose-response curve" investigation.

The particular dose-response format we used involves intensely studying one person whom we call a "study subject." The subject serves as his or her own control. In this type of study, championed by behavioral scientists, the subject goes through several study phases. In each of the phases, he or she takes a different product and undergoes multiple comprehensive metabolic evaluations during each phase. The point is to statistically compare the effects of each product to the others in their respective study phases.

All new drugs are supposed to be evaluated by dose-response curve investigations. Of course, Thyro-Gold is not a drug. It's a whole-gland dietary desiccated thyroid product. Nonetheless, our research orientation compelled us to subject the product to dose-response testing.

Why We're Reporting the Higher-than-Expected Potency Only Now. Some people who are using Thyro-Gold told us they felt that the product is stronger than other products, such as HSF. Feedback was mixed, however. Must people felt Thyro-Gold is stronger, but others didn't feel that way.

The only way to learn which people were right was to complete controlled studies involving meaningful measurements. We've now completed the initial two studies, and the evidence is clear enough. As with most studies, however, some interpretation is needed on some points. This is the case in the second study we'll soon publish. We're now about to start a different type of investigation involving a group of subjects. This study will take a few months to complete.

But for those who are interested, I want to briefly explain what was involved in conducting the two studies we're about to report in Thyroid Science. I have two reasons for giving the explaination. First, I'd like for those who use Thyro-Gold to appreciate that single-subject studies are meaningful and have provided us with important information about the product. And second, by understanding the enormous time-investiment involved, I hope they'll understand why it's taken until now to confirmation for them that Thyro-Gold is more potent that we had expected.

What was Involved in Our Initial Studies. Single-subject dose-response studies are demanding, laborious, and time-consuming. First, we had to repeatedly measure a study subject's basal metabolic rate, armpit temperature, pulse rate, and blood pressure. The term "basal" means that we took the measurements with the subject in as close to a vegetative state as possible. Otherwise, the measurements wouldn't have been meaningful and reliable. To get basal measurements, we had to take measurements either in the middle of the subject's sleep time, or immediately when he or she awoke and was in a groggy state.

Shortly after the subject woke up and was out of bed, we had to measure his or her body composition with a research-quality bioelectrical impedance instrument. Afterward, the subject fill out a series of evaluation forms.

Collecting the data for the subject's daily evaluations, however, was just the beginning of the work. We then had to score the subject's evaluation forms, and tabulate all the collected data in a spreadsheet program. After all the data was collected and tabulated, we spent days-on-end running various statistical analyses from every possible mathematical direction. The reason for the extensive data analyses was to learn everything we could of what our study data potentially revealed to us.

Last, we're preparing the manuscripts for publications that will report the two studies. Today, we're pushing to get the first study report to press, and we hope it will appear in Thyroid Science by the beginning of next week. If you haven't signed up for a free subscription to Thyroid Science, you can sign up with your email address at the homepage (www.ThyroidScience.com). That way, you'll receive email notices when the journal publishes the studies.

Our ultimate aim from these initial studies is to learn the dosage equivalence of Thyro-Gold to other products. It is the equivalences that will enable clinicians and their patients, and those who self-treat, to most smoothly transition from product-to-product. And the equivalences will enable those who understand them to better select starting dosages.

Request for Feedback from Customers. Aside from the studies I described above, we've already learned a lot about Thyro-Gold from many people who have used the product. They've kindly given us feedback on their personal experiences with the product.

We're asking for feedback from anyone who uses Thyro-Gold. We welcome it whether it's positive or negative, and the more detail the better. We're accumulating a data bank of information based on the feedback, and as soon as possible, we'll make the information readily available. We'll be immensely grateful to you if you'll help by giving us feedback on your experiences.

Finally, we sincerely hope the benefits you get from Thyro-Gold are highly satisfying to you, and we hope the product helps you recover and optimize your health. Equally important, though, we hope you'll use the product safely. All best wishes to you,

Yours sincerely,
Dr. John C. Lowe
Director of Research: Fibromyalgia Research Foundation
www.FibromyalgiaResearch.org
Editor-in-Chief: Thyroid Science
www.ThyroidScience.com
(603) 391-6061, www.drlowe.com
drlowe@drlowe.com Tammy@drlowe.com
http://www.drlowe.com/jcl/biojcl.htm

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FRANCONIA LTD

Newsletter from Dr. John C. Lowe, LLC

Thyroid & Metabolic Research and Educational Consulting — *Aug. 26, 2010*

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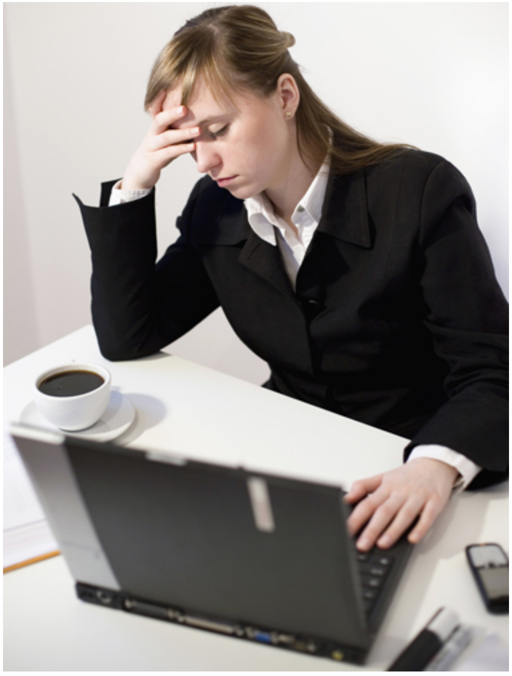
www.drlowe.com (603) 391-6061 Tammy@drlowe.com

Cortisol—too low in the day, too high at night: Resetting you cycle of cortisol secretion

Many people spend their mornings trying to "get going" with coffee. But too many people I've consulted with—even after they had one, two, or three cups of coffee, which should rouse them—are still as lethargic as the young lady to the right.

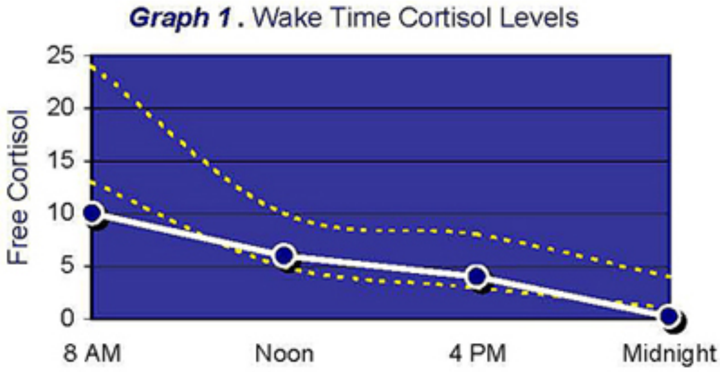
An impatient middle-aged boss is likely to look at this young lady and reach a reflex conclusion: "She partied too late last night and blew off getting enough sleep. Tough for her! She's not going to get any slack from me today!" He may be right. But maybe not. We consult with *many* people—including young ones!—whose fatigue at work is caused not by neglected sleep, but by one or two fairly easy-to-fix problems: They make far too little cortisol, or they secrete so much at night that they have too little left during the day.

For those who produce too little cortisol altogether, the fix is usually quick—that is, if they are assertive with their corrective care. A high enough dose of cortisol (but within the physiologic range) relieves some people's cortisol deficiency symptoms such as fatigue within the first week of care. For those who self treat, Isocort is the preferable product for a rapid relief. Fortunately, with what I call a "rehabilitative approach," many people need to use Isocort only for a month or two.



Adrenal Q&As at drlowe.com

But it's not people with low total cortisol output that I want to address here. Instead, it's those who produce enough cortisol overall, but secrete too much of it at the wrong time of their 24-hour cycle.

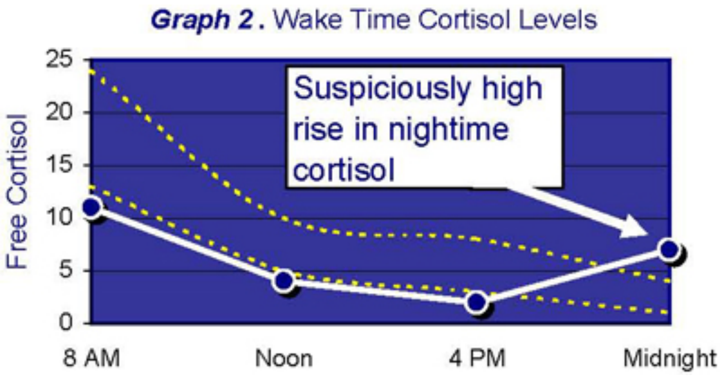


Most of you who've tested the free cortisol in your saliva have probably done it in the standard way: You took 4 saliva samples during the day: upon awaking, around noon, in the late afternoon, and just before bed. Having taken these 4 standard saliva samples, people who produce too little cortisol overall have 4 cortisol levels somewhat like those in Graph 1 (shown by the circles along the solid white line).

It's not rare, however, for a person's 4th cortisol level to be like that in Graph 2 below. I call this 4th level "suspicious." This person's cortisol levels during the daytime are obviously too low. And the rise in the late evening raises my suspicion that he or she may be secreting too much cortisol at night, which can disrupt sleep. Symptoms consistent with high nighttime cortisol, for example, are waking up repeatedly during the night, or waking up feeling like sleep hasn't been deeply restful.

Long ago, I began asking people to do a cortisol test other than the standard one that includes 4 saliva samples during waking hours. The alternate test is an 8-saliva-sample test through a full 24-hour time.

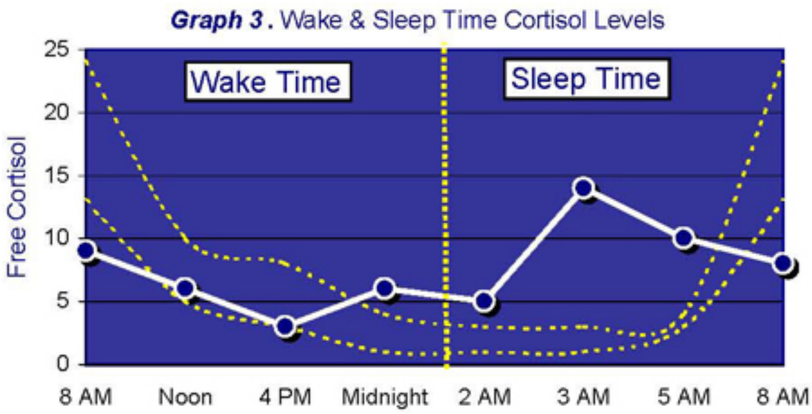
In doing the 8-sample 24-hour test, they



take the customary 4 saliva samples during the day. In addition, though, they take 3 more samples through what should be their sleep time at night. They take the last saliva sample, the 8th, upon waking (or getting up for the day) the next morning.

Often, the cortisol levels we find are like those in Graph 3 (in the right column). For most of these people, their low daytime and high nighttime cortisol levels correspond to their symptoms. For example, they are usually tired during the day and can't sleep, or can't sleep restfully, during the night. Fortunately, the fix I recommend for this abnormal circadian cortisol rhythm, Seriphos, is relatively inexpensive and usually works well. But I'm getting ahead of myself (more about Seriphos below).

Taking Saliva Samples at Night. If you wake up repeatedly through the night, taking the 3 nighttime saliva samples may be no problem for you. You may wake up plenty enough times to take the samples. You should keep cold water close-at-hand. Before taking the nighttime saliva samples (just like during the day), you should hold the cold water in your mouth for a minute or two. Hopefully, you can then drift back off to sleep at least for a while.



In Graph 3 above, the person's nighttime cortisol levels are higher than her daytime levels. When factors such as shift-work don't interfere, Seriphos may lower the nightime levels. This will leave her with more cortisol in reserve to be secreted during the stresses of her days. Her 24-hour cortisol levels will then resemble those in Graph 4 below.

If you don't wake up repeatedly through the night, having a caring loved one who'll gently wake you is optimal. However, you may have to set a soft cell-phone alarm that gently rouses you from sleep. Of course, you don't want to use a loud alarm that startles you out of sleep.

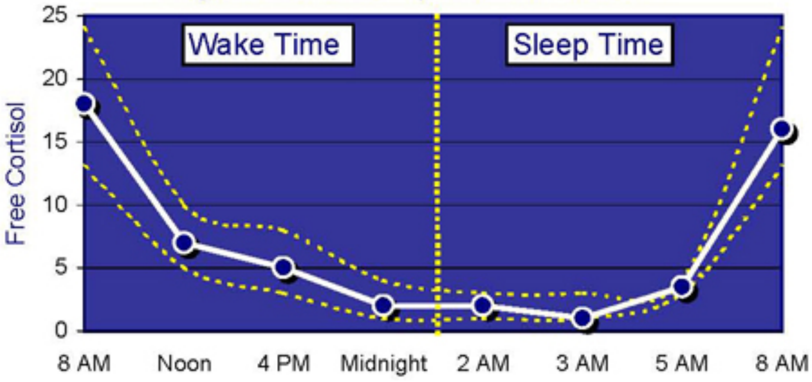
A potential criticism of the nighttime sample-taking is that artificially waking yourself may raise your cortisol level. That's true. But consider this: If your cortisol levels in your daytime samples are low (as in Graph 3 below), secreting an *appropriate* amount in response to an alarm at night shows us exactly what we want to know: That is, do you have an abnormal circadian secretion of cortisol? Do you make enough cortisol and hold it in reserve during the day, and for some reason secrete it readily at night? Or do you produce a normal amount of cortisol but have little left during the day after secreting too much too easily at night?

Resetting Your Cycle of Cortisol Secretion. If you turn out to have high cortisol at night and too little left for the day, you may be able to reset your pattern of cortisol secretion. Your aim, of course, will be to bring about optimal cortisol levels during your whole 24-hour cycle.

This optimal pattern is roughly shown in Graph 4 (below). In this pattern, cortisol is low enough during sleep so that it doesn't interfere with sleep. Then upon waking, cortisol secretion is at its highest point. The level should then decrease during the rest of the day and evening, with one exception. During stresses even late in the day, you want to have enough cortisol in reserve to provide an adaptive cortisol spike.

Seriphos or Phosphatidyl Serine. The product I recommend for resetting one's cycle of cortisol secretion, as I mentioned above, is "Seriphos." This product contains the amino acid "serine" bound to pure phosphorus. (Seriphos is technically called phosphorylated serine. The term "phosphorylated" is pronounced fos' fŏr' i lāted.) The product also contains a synergistic compound called "ethanolamine."

Graph 4. Wake & Sleep Time Cortisol Levels



Recovering reasonably normal cortisol levels during the day and night isn't easy for someone troubled by high nighttime cortisol. For example, a person's cortisol can be high too much of the night because of low blood sugar levels at night. Seriphos might help this person sleep better, but the proper solution in her high nighttime cortisol is to arrange to have normal blood sugar levels through the night. The scenario I've presented in this article, then, is "cleaner" than some people's effort to lower their cortisol levels at night. But many people's cases have been as clean as this scenario. It is from those people's successes with Seriphos (sometimes used in conjunction with Isocort) that I composed this article.

Seriphos usually isn't sold at health food stores and most pharmacies. At those outlets, you'll usually find a related product called "phosphatidyl serine." (Phosphatidyl is pronounced fos' fō tid' l.) This product works as well as Seriphos, but I recommend Seriphos for several reasons.

Cost & Composition. My first reason for preferring Seriphos over phosphatidyl serine is one of great importance to steadily more people today—that is, cost. In general, Seriphos is substantially less expensive than phosphatidyl serine.

The serine in Seriphos is from vegetables and the phosphate is pure. In contrast, the phosphorus in phosphatidyl serine is typically derived from soy. Many of the people we consult with have sensitivities to soy or actual soy antibodies. In avoiding soy-containing products, these people avoid phosphatidyl serine.

Work Load. Phosphatidyl serine is actually a precursor of the active compound in Seriphos, phosphorylated serine. Before being absorbed into the blood from the GI tract, phosphatidyl serine has to be partially digested to phosphorylated serine. It's helpful to consider that 100 mg of phosphatidyl serine yields about 20 mg of phosphorylated serine.

To convert phosphatidyl serine to the phosphorylated form, pancreatic and intestinal brush-border enzymes have to partially decompose phosphatidyl serine. The activity of those enzymes expends energy, energy that isn't required to absorb the ingredients in Seriphos. Moreover, the phosphorylated serine in Seriphos absorbs more easily because it's chelated to calcium and magnesium.

In breaking down phosphatidyl serine in the GI tract, enzymes cleave from phosphatidyl serine two fatty acids and a molecule of glycerol. What remains to be absorbed is the phosphorylated serine, as in Seriphos. The phosphorylated serine absorbs into the blood and then enters cells. Inside cells, glycerol and two more fatty acids are added back to the molecule. The fatty acids, however, are usually different from those that were broken off in the GI tract. The fatty acids that attach to phosophorylated serine are ones that are appropriate to the particular type of cell.

Dose. In working to reset their cycle of cortisol secretion, we recommend that most people start with 2 capsules of Seriphos. If this dose doesn't improve sleep, we suggest an increase to 3 capsules, and if necessary, 4 capsules. The most capsules anyone has told us he needed to sleep well and recover a normal cortisol secretion pattern was 6 per night.

Unfortunately, we don't have research data that tells us the time needed for Seriphos or phosphatidyl serine to reset the day time and night time cortisol secretion pattern. However, Seriphos works well for most people with high night time cortisol, and follow-up tests have shown that the product can help bring about a cortisol secretion pattern like that in Graph #4.

If you reduce your cortisol secretion enough through the night, you may have enough cortisol in reserve to meet your needs through the day. If so, you won't need to take Isocort during the daytime.

You may have a clinician who is experienced in using Seriphos and Isocort. If so, you may feel most comfortable consulting him or her before beginning your regimen of self-care. If you don't have a suitable local clinician, then I *strongly* recommend the soundly rational approach for all of us who are involved in self care: read, read, read, and continue reading, and while doing so, question the accuracy of *everything* any writer expounds upon, especially if he or she is a doctor. (You can start, as you should, by questioning the veracity of my views in this article.) You'll find many conflicting viewpoints, but don't let that discourage you. Instead, let it muster your resolve to keep on reading, questioning, and exercising your very best discretion to decide what to *you* best corresponds to the facts and makes the most sense. Tammy and I wish you the very best.

Adrenal Q&As at drlowe.com

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Our Educational Consulting Service

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Newsletter from Dr. John C. Lowe, LLC

Thyroid & Metabolic Research and Educational Consulting — *Sept. 12, 2010*

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www.drlowe.com (603) 391-6061 Tammy@drlowe.com

It May Soon be *Painless* to Learn if High or Low Blood Sugar is an Obstacle to Effective Thyroid Hormone Therapy for You

In my early years of clinical practice, I often sent patients to local medical labs to undergo glucose tolerance tests. Many patients came back from the lab describing their bad reactions to the 75 grams of pure glucose lab techs had them swallow. Besides feeling bad about their unpleasant experiences, I never felt that the blood sugar pattern produced by pure glucose was the pattern the patients had in response to their usual carbohydrate meals.

For these two reasons, I long ago developed instructions for my patients to do a home glucose tolerance test. For short, we call it the "hGTT."

The instructions we send to a person guides him or her through a 6-hour test during which he or she takes 8 blood samples. The point to the test is to observe on a line graph how the person's blood sugar behaves in response to a carbohydrate meal of about 75 grams of carbohydrates. To do the test, the person uses a inexpensive glucometer. And in doing so, he or she must use lances with needles at the end to prick the skin to bring up a spot of blood to the surface of the skin. Then he or she touches a test strip sticking out of the glucometer to the spot of blood, and the glucometer measures the sugar level of the blood at that designated time during the test.

Doing this home test doesn't involve the nausea and other upsets that so many patients experienced during lab glucose tolerance tests. But people who do the test do still experience a brief pain from the skin prick with the needle. In the near future, though, the prick and pain may be an experience of the past.

Microwave-Beam Device to Measure Blood Sugar. Baylor University researchers are now working on a needle-free method of measuring blood sugar levels. The researchers recently announced that they've developed a portable device that sends electromagnetic waves through the skin to measure blood sugar levels. Hopefully the device will soon be on the market.

When the device is available, people will no longer have to repeatedly stick their skin with needles. With the needle-prick induced pain, they can learn whether high or low blood sugar may be preventing them from taking a high-enough dose of thyroid hormone to get fully well.

Why the hGTT is Important. The hGTT is probably the most valuable test I've ever asked people to do. Most of those who’ve done the test have had high sugar levels. Traditionally, clinicians have called such high sugar levels "glucose intolerance" or "hyperglycemia."

To illustrate the importance of the hGTT, consider a hypothyroid person who also has high blood sugar. Consider that the person drives the energy metabolism in her cells with a minimally effective dose of thyroid hormone. If her cells have too little glucose because it’s suspended in her blood for too long, she may experience a sort of crisis in the cells of the hypothalamus in her brain. That is, the thyroid hormone (too little for her to get well) stimulates the production of enzymes that trigger the chemical reactions of energy metabolism. At the same time, though, she has too little sugar in the cells of the hypothalamus to provide the electrons that are absolutely essential to normal energy metabolism.

In response to this energy crisis, the hypothalamus activates the sympathetic nervous system, the emergency part of the nervous system. Sympathetic nerves release adrenaline and noradrenaline. These two neurotransmitters then stimulate liver and muscle cells to break down their stored starch to provide glucose, which is released into the blood. This will raise her blood sugar higher, but if she doesn’t have enough insulin or insulin receptors on her cells, too much of the sugar will stay in her blood, raising it further. And her hypothalamus—still deprived of enough sugar—may sustain the release of adrenaline and noradrenaline from sympathetic nerves.

Her symptoms during this process—caused by the adrenaline and noradrenaline—may be mistaken for overstimulation by too much thyroid hormone, or “thyrotoxicosis.” She’s likely to experience symptoms such as tremors, anxiety, nervousness, headaches, rapid heart rate, and waves of body heat and sweating. From her symptoms, she and her clinician may even suspect that too much thyroid hormone is causing panic attacks.

Of course, her unpleasant symptoms are produced by the interaction between her thyroid hormone intake and her high blood sugar. But it’s usually thyroid hormone that’s ajudged the perp. But if she lowers her thyroid hormone dose, and this relieves the adrenaline-induced crises, she’ll still suffer from symptoms of hypothyroidism. Thyroid hormone obviously took part in her crises, but it wasn’t the primary culprit. Instead, her high blood sugar was.

The way we’ve helped people out of this dilemma is to teach them how to identify their high blood sugar with the hGTT. We then teach them how to correct the blood sugar problem by using over-the-counter natural medicinal agents, which clinical trials have shown are highly effective. And after correcting the underlying problem of high blood sugar, she should be able to move her thyroid hormone dose high enough to fully recover from her hypothyroid symptoms.

John C Lowe

Tammy@drlowe.com

Our Educational Consulting Service

We provide educational consulting to both patients and clinicians. Phone us at 603-391-6061, or preferably, write to us at Tammy@drlowe.com. Our fax number is 303-496-6200.

—Tammy Lowe

Your doctor won't order the lab tests you want? Then order the tests yourself. *In fact, order* any *lab test you want at discounted fees:* www.directlabs.com/drlowe. Thyroid tests are markably discounted, including the TSH, T3, T4, thyroid peroxidase, and thyroglobulin antibodies.

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Newsletter from Dr. John C. Lowe, LLC

Thyroid & Metabolic Research and Educational Consulting — *Nov. 18, 2010*

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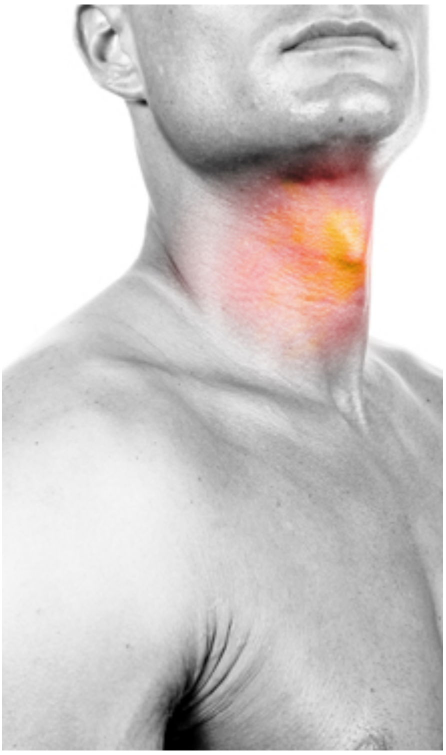
www.drlowe.com (603) 391-6061 Tammy@drlowe.com



Ways to Lower or Extinguish the Inflammation of Auto-immune Thyroiditis

For decades, I've consulted with countless people who've had auto-immune thyroiditis. Some of have a form called "Graves' disease." They've had thyroid stimulating anti-bodies and thyroid hormone overstimulation.

I deal with this autoimmune thyroid topic elsewhere at drlowe.com. You can reach it by using the "find" window above. Or you can find the topic listed at our Q&A menu page.

Here, I want to deal with the two anti-thyroid antibodies called "thyroyid peroxidase" and "thyroglobulin" antibodies.

These two antibodies can destroy the ability of the thyroid gland in producting thyroid hormone. They can thus lead to hypothyroidism. And, of course, as I explain in the left column of this page, a recent study indicates that high thyroglobulin antibodies are associated with thyroid cancer. This is especially true in male patients.

Let's Just Watch It Until it Causes Health Problems. This is what many patients with high anti-thyroid antibodies hear from their clinicians, especially endocrinologists: "Let's just wait until you're really having trouble from the disease, and then we'll maybe start you on some T4."

The problem is, many of these people already have health problems associated with the high antibodies. Their thyroid glands are inflamed. The fact that they have high anti-thyroid antibodies is proof positive of that. With inflamed thyroid glands, some people feel pressure in their necks from enlargement of their thyroid glands. And they feel a swelling in the fronts of their necks when they swallow. Some may feel that they fronts of their necks are warm or even hot. And many of the people already feel troubling or even debilitating symptoms of hypothyroidism.

It's the people's symptoms from the inflamed glands that drive most of the people to get seek professional help. What too many get instead is attention from their clinicians that's lackadaisical at best.

Not only is the inflammation the cause of the nigh anti-thyroid antibodies. As they note, inflammation takes part in the formation of cancerous tumors.[1,p.3] And they state, "Chronic tissue inflammation is associated with an increased risk of tissue specific malignancy."[2,3,4]

In that inflammation or something associated with it can lead to thyroid cancer, it's prudent of your clinician(s)—and especially, it's wise of you—***not*** to exercise patience. If you do, you just wait for the hammer of "let's-wait-and-see-what-happens" to slam down on your health and well-being.

What to Do. So what is prudent to do in the way of prevention? In that inflammation is the cause of anti-thyroid antibodies and malignancies, my approach is a strongly anti-inflammatory one.

I recommend is five steps:

- Test your anti-thyroid antibodies to learn if they are high. If your clinician(s) won't order them, then order them yourself at discounted fees through our portal at www.directlabs.com/drlowe. (see details below).

- If you have high antibodies, take a high-enough dose of thyroid hormone to lower your TSH and allow your thyroid gland to atrophy to some degree. This will provide less overall thyroid gland inflammation and fewer thyroid for antibodies to attack. By the way, when I mention taking enough thyroid hormone, I do *not* refer to taking any brand of T4 alone. People do best with products that contain either T4/T3 in combination, or prompt-release T3 and not sustained-release T3.

  For full understanding of how safe and effective thyroid hormone affects can augment the function of your immune system, read the pdf chapter from *The Metabolic Treatment of Fibromyalgia.* It's available through the publisher as a standalone pdf chapter. When you reach the e-chapter page, scroll down to the immune chapter: Chapter 3.13Immune Dysregulation.

- Make sure you have enough anti-inflammatory cortisol. Today, salivary free cortisol levels is the superior lab test approach—despite the fact that many clinicians are stuck in mid-20th century thinking and unscientifically "don't believe in salivary testing." Leave these anachronistic clinicians stuck in the ancient past, like the snails, gophers, and saber-tooth cat preserved in the La Brae tarpits of Los Angeles. Instead, move on and avail yourself of modern laboratory scientific advancements.

  Your daytime and nighttime free saliva cortisol levels should look close to the levels in the graph below. (To see what your cortisol levels whould best look like, see our August 27, 2010 newsletter.)

- Adopt and stick to an anti-inflammatory diet. This means either a cave person diet or one of the many rich Mediterranean diets, including food like that to the right. These diets are so varied and so health-inducing and health-sustaining that once you adopt them for your own, you're likely to find the pro-inflammatory traditional American-type diet repugnant and easy to reject.

- Take an array of anti-inflammatory nutrients, herbs, and other botanicals. Some include omega-3 fatty acids; Boswellia; ginger; turmeric; glucosamine; chondroitin; and a strong raw-foods, organic multivitamin supplement like Franconia's New Life Multi.

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Tammy@drlowe.com

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Thyroid Science 4(8):R1-5, 2009

Iodine: the Forgotten Weapon Against Influenza Viruses

Full Text Free in pdf format

David Derry, MD, PhD
332 – 425 Simcoe Street
Victoria BC V8V 4T3

Correspondence: Dr. David Derry dderry@shaw.ca

Background. After the 1918 Influenza Pandemic which killed an estimated 30 million people, governments financed research on the Pandemic's causes. Over 25 years, influenza viruses were isolated and methods for killing them with various agents discovered. Iodine was the most effective agent for killing viruses, especially influenza viruses. Aerosol iodine was found to kill viruses in sprayed mists, and solutions of iodine were equally effective. In 1945, Burnet and Stone found that putting iodine on mice snouts prevented the mice from being infected with live influenza virus in mists. They suggested that impregnating masks with iodine would help stop viral spread. They also recommended that medical personnel have iodine-aerosol-treated rooms for examination and treatment of highly infected patients. Current methods of dealing with influenza infection are isolation, hand washing, antiviral drugs, and vaccinations. All of these methods can be improved by incorporating iodine into them. When impregnated with iodine, masks become much more effective, and hand washing is more effect when done with mild iodine solutions. Isolation techniques coupled with aerosol iodine would make them safer for patients, medical personnel, and all persons working with the public. Public health authorities could organize the distribution of iodine and at the same time educate the public in the effective use of iodine. Oral iodine might also boost body defense mechanisms in the upper oral and respiratory mucus. Conclusion: Iodine incorporated into masks, solutions, aerosols, and oral preparations could help to kill influenza viruses and fight off an H1N1 Pandemic.

Keywords. H1N1 • Influenza virus • iodine • aerosols • immunization • isolations • masks • prevention

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Iodine: the Forgotten Weapon Against Influenza Viruses

David Derry, MD, PhD

332 – 425 Simcoe Street
Victoria BC V8V 4T3

Correspondence: Dr. David Derry dderry@shaw.ca

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Abstract. After the 1918 Influenza Pandemic which killed an estimated 30 million people, governments financed research on the Pandemic's causes. Over 25 years, influenza viruses were isolated and methods for killing them with various agents discovered. Iodine was the most effective agent for killing viruses, especially influenza viruses. Aerosol iodine was found to kill viruses in sprayed mists, and solutions of iodine were equally effective. In 1945, Burnet and Stone found that putting iodine on mice snouts prevented the mice from being infected with live influenza virus in mists. They suggested that impregnating masks with iodine would help stop viral spread. They also recommended that medical personnel have iodine-aerosol-treated rooms for examination and treatment of highly infected patients. Current methods of dealing with influenza infection are isolation, hand washing, antiviral drugs, and vaccinations. All of these methods can be improved by incorporating iodine into them. When impregnated with iodine, masks become much more effective, and hand washing is more effect when done with mild iodine solutions. Isolation techniques coupled with aerosol iodine would make them safer for patients, medical personnel, and all persons working with the public. Public health authorities could organize the distribution of iodine and at the same time educate the public in the effective use of iodine. Oral iodine might also boost body defense mechanisms in the upper oral and respiratory mucus. ***Conclusion:*** Iodine incorporated into masks, solutions, aerosols, and oral preparations could help to kill influenza viruses and fight off an H1N1 Pandemic.

Keywords. H1N1 • Influenza virus • iodine • aerosols • immunization • isolations • masks • prevention

Influenza Pandemic History

The 1918 Influenza Pandemic killed an estimated 30 million people within a year. In the quarter century following the Pandemic, governments financed intensive research into the Pandemic's causes and treatments for the viruses that cause influenza.[1] Iodine was the superior antiseptic that at low concentrations killed the airborne viruses that cause influenza. Iodine was without toxicity.[2-12]

The 1918 Pandemic was unusual in that it affected young healthy men, especially soldiers.[1] Normal flu infections are most virulent against young children and older persons.[14] H1N1 virus also concentrates its lethality on young healthy persons between ages 5 and 18, as reported by Dr. Thomas Frieden, director of the U.S. Centers for Disease Control and Prevention.[13-14] In this manner, the H1N1 virus resembles the 1918 virus.

The 1918 virus attacked again in the fall and over two-months killed millions of people. It is anticipated that the H1N1 virus may behave similarly, and public health authorities and the medical profession are bracing for this potential outcome.

Treatment and Prevention

The time-tested weapons against influenza viruses are cleanliness, hand washing, isolation, masks, immunizations, and antiviral medications. In 1918, the last two were not available, and the other methods did little to stop viral spread. Washing hands in a standard 70% alcohol solution is effective against most pathogenic bacteria, but it has no effect on viruses, especially influenza viruses.

In a similar manner, masks used in 1918 showed barely detectable benefits in holding back influenza spread as viruses readily passed through the gauze. Isolation is difficult to institute and enforce in cities with large numbers of infected patients. In sparsely-populated communities such as Alaska, isolation was beneficial but difficult to implement. Even in hospitals, large numbers of patients tend to overwhelm and compromise isolation techniques.[1]

Vaccines and antiviral drugs have been prepared and are available in many Western Countries. These interventions are of unknown benefit, as influenza viruses tend to mutate rapidly.

Iodine

Iodine is the most effective broad-spectrum antiseptic with low toxicity.[21] Iodine has very high germicidal activity, and no organism develops resistance to iodine.[12]

Iodine has been used in various forms as an antiseptic for the skin, wounds, and mucous surfaces of the body. It has also been used to sterilize the air and inanimate objects such as catgut and surgical instruments. Moreover, it has been used as a prophylactic and therapeutic agent in diseases caused by bacteria, viruses, and fungi, and to sanitize eating utensils.[7,12] Iodine kills bacteria, viruses, fungi, protozoa, and even spores of bacteria and fungi, including anthrax spores. Iodine was used successfully against influenza, herpes, small pox, and chicken pox viruses.[7]

When iodine was suspended in a solution, viral inactivation occurred at dilutions of 1/1,000,000. Aerosols inactivated many viruses within 30 seconds or less.[7,8,12] Watery solutions such as Lugol's are the superior germicides.[12]

New Findings Leading to Effective Therapy with Iodine

In 1945, a breakthrough occurred when J.D. Stone and Sir McFarland Burnet (who later went on to win a Nobel Prize for his Clonal Selection Theory) exposed mice to lethal effects of influenza viral mists. The lethal disease was prevented by putting iodine solution on mice snouts just prior to placing them in chambers containing influenza viruses.

Burnet and Stone wrote, "As a protection for doctors, nurses and others dealing with highly infectious patients (Pandemic Influenza) it should be relatively easy to design a gauze mask partially impregnated with iodine which should offer a greatly increased degree of protection to the wearer."[2,3]

Burnet and Stone also suggested, "it may be worth considering iodine vapor as a practical means of limiting indoor infection during an influenza epidemic"[2,3] Students in classrooms were protected from influenza by iodine aerosol therapy. Aerosol iodine also is effective against freshly sprayed influenza virus.[8]

Iodine Body Properties and Distribution

Iodine has been known as a universal antiseptic for 150 years and has few side effects except in high doses. Iodine was introduced into our diets with iodized salt by David Marine in 1920.[21,26] This effectively eliminated goiter, cretinism, and mental retardation caused by inadequate iodine in our diet.[21,27,28]

Extremely high doses of iodine can have serious side effects, but only a small fraction of such extreme doses are necessary to kill influenza viruses. Iodine circulating in the blood is captured by many tissue sites and ends up in mucus secretions. The tissues include thyroid and salivary glands, nasal secretions, stomach, and lungs. Collectively, these tissues and mucus products contain free iodine which defends against invasion by bacteria and viruses.[16,20]

When dietary iodine is absorbed from the gut all the above sites along with urinary output compete for blood iodine. The most potent competitor is the thyroid glands, which uses iodine to make thyroid hormone. A constant percentage of dietary iodine is excreted in the urine.[16]

Upper Respiratory and Oral Mucus Defenses

The salivary glands, nasal mucosa, and lungs all secrete mucus which contains iodine.[16] The lungs not only secrete mucus, but Salter thought volatile iodine mixes with alveolar air to enter the bronchioles.[17] If this is occurs, it would serve as an additional barrier to the invading air borne viruses in a manner similar to aerosol iodine.

Stomach mucosa captures iodine from blood and secretes it into stomach cavities. Free iodine in the stomach kills bacteria and viruses and it deactivates biological and chemical toxins. Dead viruses are still immunologically competent and thus antibodies can be made to dead viruses.[20, 22] Overall, we see there is a complex integrated system for protecting humans from viral or bacterial invasions via oral, nasal, and gastrointestinal routes.[16] This system depends on taking adequate iodine orally.

Current Iodine Doses and Doses Needed to Prevent Invasion

Our current recommended iodine intake by the WHO is 150 to 200 micrograms daily. This dose first started by David Marine in 1920 has successfully prevented goiters, cretinism, and mental retardation.[21] If the daily iodine dose is above 3 mg for over 2 weeks, the thyroid gland becomes saturated and no longer takes up much iodine.[25]

Then, dietary iodine goes to other sites named above and is excreted into the upper respiratory and gastrointestinal tract mucus.[16] It seems logical that air borne viruses become stuck in mucus and killed by free iodine.

Dietary iodine found in iodized salt is below the amounts needed to fill mucus defense roles. To protect themselves, people wishing to boost their defense against infections should supplement their diets with iodine in the form of Lugol's. Most people will probably be protected by an amount of Lugol's that provides the average amount of iodine ingested by Japanese populations for centuries. This amount is about 12 mg daily. Two drops of Lugol's daily in the liquid of their choice will provide 13 mg.

Lugol's Iodine Solution

Lugol's iodine solution was discovered by Henri Lugol, a Paris physician,[21] more than 150 years ago. It has been used therapeutically since then. Lugol's consists of 5% free iodine and 10% potassium iodide in water. Lugol's has a distinct advantage over most other iodine oral medications by having a high level of free iodine, which is the active ingredient that kills viruses.[5,6,15]

Medical personnel and others interacting with highly infectious persons should consider protecting themselves with 2 drops daily of Lugol's iodine orally in the liquid of their choice, as all liquids work. At this dose, no noticeable side effects occur.

Free iodine is believed to react with the amino acids tyrosine and/or histidine at low concentrations. The reaction denatures proteins and causes the death of cells.[5,6,20,22] In Canada, Lugol's iodine solution can be bought over the counter and costs about 10 dollars for 100 ml. This amount will last one person 5 years.

Iodine Well Tolerated by Humans

With few exceptions, humans tolerate well large doses of iodine.[18-24,29] High doses are not required to kill viruses. Aerosols can be effective in sterilizing a room at levels not detectable by humans.[7,4,8,12] In the 1930s, iodine's use therapeutically was stated in the US Pharmacopeia. The usual dose for treatment is 300 mgs (46 drops of Lugol's) to 1 gm (1000 mg, 154 drops). The maximum safe dose in 24 hours should seldom exceed 6 gm as at these extreme doses iodine is not without danger. Such high doses are not needed to prevent or treat influenza virus infections.

Educating the Public

Supervised by Public Health Officials and physicians the lay public can be taught ways to use iodine. By using iodine correctly persons could protect themselves and their families. Stock piled concentrated solutions can be the source of more dilute solutions for distribution to the public.[7,12]

Can Lugol's be Given to Treat Influenza Infection?

The author is not aware of any published data on treating viral infections with oral or intravenous Lugol's solution or any other medications with the exception of some topical iodine's use for herpes infections. As Lugol's is well tolerated both ways, it is a form of treatment that could be explored. It was standard practice to give high doses of iodine for Graves' disease prior to thyroidectomy and no serious side effects were noticed.[24]

Why Did the Japanese not Fair Better in the 1918 Influenza Pandemic?

A possible explanation for Japanese citizens doing as badly as the rest of the world in 1918 is that in Japan, as well in Chile, citizens have the highest consumption of nitrates in the world. Nitrates in high doses competitively block membrane transport mechanisms that move iodine from the blood into the thyroid gland, salivary glands, and stomach mucus glands. This nitrate effect would interfere with body defense systems. No opportunity has arisen to test this possibility.

Pre-planning in Catastrophes

Hard, fast, and exacting rules for preventing an Influenza Pandemic cannot be laid down. However, definite, prearranged, overall systematic planning is necessary. All possible methods of prevention and intervention should be taken into consideration so that the greatest amount of good to the largest number of people results.[12]

The methods using iodine are untried in pandemic conditions. It is likely that trying the methods during pandemic will present new problems. Nor are these proven methods of protection, as no epidemic has been tested this way. However, data reviewed here indicate that this approach, done properly, could help arrest an epidemic and possibly save many lives, especially those of medical personnel, from this horrible disease.

For stock piling, it is more economical to store a supply of a mixture of iodine and a soluble iodide in glass bottles. The bottle sizes should be such as to make quickly available solutions of desired concentrations of free iodine without the necessity of weighing at the time of use. In this form the germicide shelf life is indefinite.[12]

Conclusion

A medical literature review indicates the 1918 Influenza Pandemic was caused by viruses. In addition, iodine, as iodine solutions or aerosols, was superior in every respect to kill the flu viruses. These findings indicate that simple methods could help with the fight if an epidemic occurs.

Many forms of iodine have been available, but Lugol's iodine has stood the test of time and is standardized around the world. Lugol's has advantages. It has a high free iodine content, which suggests it may be a choice agent for fighting influenza virus. Using iodine has not been tried, but available data strongly suggests it should help.

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Inadequate Thyroid Hormone Regulation as the Main Mechanism of Fibromyalgia: A Review of the Evidence

John C. Lowe †Δ **and Jackie Yellin**‡

Directors of Research† and Education‡: Fibromyalgia Research Foundation

Δ*Contact*: Dr. John C. Lowe, 19 Long Springs Place, The Woodlands, TX 77382, U.S.A.
drlowe@FibromyalgiaResearch.org

Abstract. All symptoms and most objectively verified abnormalities among fibromyalgia (FMS) patients are characteristic of subsets of patients with hypothyroidism or partial peripheral thyroid hormone resistance. Laboratory tests have shown a higher-than-normal incidence of thyroid disease among FMS patients. Among 40 objectively verified abnormalities that also occur in hypothyroidism and peripheral thyroid hormone resistance, FMS patients have abnormally low resting metabolic rates and basal body temperatures. In several open and blinded treatment trials, thyroid hormone therapy other than T_4-replacement has reduced or eliminated FMS symptoms and many study patients have ceased to meet the criteria for FMS. In addition, a 1-to-5-year follow-up study showed that patients treated with thyroid hormone remained improved and used fewer medications to control symptoms than did matched untreated controls. These study findings constitute rigorous testing of, yet failure to refute, the inadequate thyroid hormone regulation etiological hypothesis of FMS.

Competing etiological hypotheses of FMS account for only a fraction of the symptoms and objectively verified abnormalities among patients, and no treatment other than thyroid hormone therapy has been shown to relieve patients of FMS status. This review of the published research literature shows that inadequate thyroid hormone regulation is the most likely underlying mechanism of the symptoms and objective abnormalities of patients who meet the criteria for FMS.

Key Words. Basal body temperature, Fibromyalgia, Free T_3, Free T_4, Resting metabolic rate, Thyroid antibodies, TSH

Introduction

"Fibromyalgia syndrome" (FMS) is the diagnosis clinicians most often give patients who have chronic widespread pain and abnormal tenderness. Most FMS researchers state that the etiology of the disorder is unknown. In doing so, they fail to account for a substantial line of evidence showing that the main mechanism of FMS is inadequate thyroid hormone regulation.

In 2004, Wallace and Clauw published a book titled *Fibromyalgia & Other Central Pain Syndromes*.[30] Wallace and Clauw, chapter authors in—and editors of—the book, are central figures in the clique that continues life support for the decerebrated rheumatology paradigm of FMS.[1,pp.57-91] Their book can be fairly considered the latest update on the authors' knowledge of FMS, its mechanisms, and it treatments.

To say that these editors and chapter authors gave short shrift to inadequate thyroid hormone regulation of cell function as a putative etiological hypothesis of FMS would be a gross understatement. The terms "hypothyroidism" and "thyroid hormone" are not listed in the index of the book. In his chapter titled "Fibromyalgia in Inflammatory and Endocrine Disorders," Hallegua devotes two short paragraphs and one concluding sentence to hypothyroidism. In the concluding sentence he wrote, "Thus there is no conclusive evidence of specific thyroid dysfunction in FMS syndrome [sic], although it remains an important diagnosis to exclude when making the primary diagnosis."[31,p.190]

One purpose of this review is to counterbalance what I interpret as the 2004 book's editors' and authors' gross neglect of the published scientific literature on the relationship of thyroid hormone to FMS. Despite their neglect, I contend that the evidence I cite below indicates that the main underlying mechanism of most patients' FMS is inadequate thyroid hormone regulation of cell function.

Line of Evidence

The evidence that too little thyroid hormone regulation of cell function is the main underlying mechanism of FMS falls into four categories. These are: (1) symptoms, (2) studies of thyroid test results, (3) objectively verified abnormalities among patients, and (4) clinical trials with thyroid hormone therapy.

Symptoms

As many clinicians and researchers have reported,[1][2][3][4][5][6][7][8][9][10][11][12][13][14][15][16][17][209] FMS patients' symptoms are identical to those of a subset of patients who have either hypothyroidism or the "peripheral" form of thyroid hormone resistance. The patients' predominant symptoms are chronic widespread pain and abnormal tenderness. These two symptoms are considered essential to a diagnosis of FMS. But along with these symptoms, which are classic for a subset of patients with inadequate thyroid hormone regulation, most FMS patients also have other symptoms.

Table 1 lists the symptoms that rheumatology-paradigm FMS researchers term "associated symptoms" of FMS. Other clinicians use a different terminology: they state that when some hypothyroid patients first consult them, the patients do so with "presenting" symptoms of FMS.[209] To clinicians intimately familiar with the three relevant clinical categories (hypothyroidism, peripheral thyroid hormone resistance, and FMS), the symptoms of many patients in any one of the categories are indistinguishable from those of many patients in the other two categories.

Studies of Thyroid Test Results

In primary hypothyroidism, a thyroid hormone deficiency results from failure of the thyroid gland to produce adequate thyroid hormone. In central hypothyroidism, the patient's thyroid gland produces too little thyroid hormone for another reason: one or both of the two structures in the brain that regulate the thyroid gland (the hypothalamus or the pituitary gland) is malfunctioning. As a result, the thyroid gland does not produce an optimal amount of thyroid hormone. FMS patients as a group have a high incidence of thyroid function test results showing "primary" or "central" hypothyroidism.[20][21][22][23][24][25][26]

FMS patients also have a higher incidence of antithyroid antibodies than people at large.[18][19] High antithyroid antibodies means that a patient's thyroid gland is undergoing a destructive autoimmune process. In Hashimoto's thyroiditis (struma lymphomatosa),[214] suppressor T-lymphocytes are reduced. Helper T-lymphocytes increase in the interstitial spaces between the gland's follicles. This is followed by infiltration of the gland by B-lymphocytes and plasma cells. The gland's follicles then atrophy and fibrosis accumulates.[212][215,p.921] The B-lymphocytes and the plasma cells derived from them secrete antibodies against either or both the gland's thyroglobulin and thyroid peroxidase.[213] The gland itself is the major site of thyroid antibody production.[216]

Table 1. Most common symptoms associated with FMS.*λ

SYMPTOM	% OF PATIENTS WITH THE SYMPTOM
Widespread pain	97.6
Fatigue	81.4
Morning stiffness >15 min.	77.0
Sleep disturbance	74.6
Paresthesias	62.8
Headache	52.8
Anxiety	47.8
Sensation of swelling	47.0
Dysmenorrhea history	40.6
Sicca symptoms	35.8
Prior depression	31.5
Irritable bowel syndrome	29.6
Urinary urgency	26.3
Raynaud's symptoms	16.7
Female urethral syndrome †	12.0
Cognitive dysfunction ‡	—

*After: Wolfe, F.: Diagnosis of fibromyalgia. *J. Musculoskeletal Med.*, 7:54, 1990.[136]

λ Originally published in Lowe, J.C.: *The Metabolic Treatment of Fibromyalgia*. Boulder, McDowell Publishing Co., 2000, p.785.[1]

†Yunus, M.B. and Masi, A.T.: Fibromyalgia, restless legs syndrome, periodic limb movement disorder, and psychogenic pain. In *Arthritis and Allied Conditions: A Textbook of Rheumatology*. Edited by D.J. McCarty, Jr. and W.J. Koopman, Philadelphia, Lea & Febiger, 1992, pp.1383-1405.[210]

‡Nielson, W.R., Grace, G.M., Hopkins, M., and Berg, M.: Concentration and memory deficits in patients with fibromyalgia syndrome. *J. Musculoskeletal Pain*, 3(Suppl.1):123, 1995.[211]

NOTE: The reported frequency of different symptoms varies according to source.

At some point in this destructive process, the gland ceases to produce enough thyroid hormone on average to maintain normal metabolism and health. The patient can then develop symptoms of hypothyroidism without elevated blood thyroid antibodies.[185][186][187][188][189] Moreover, the patient with autoimmune thyroiditis (with or without symptoms) may have reference range TSH and thyroid hormone levels for years.[215,p.927] A significant percentage of FMS patients, especially females, with high antithyroid antibodies but "normal" TSH and thyroid hormone levels have chronic, widespread pain that is often diagnosed as "fibromyalgia."[15]

Before 2002 in the United States, researchers (based on a higher-than-current upper limit for the TSH) calculated that the incidence of primary hypothyroidism in the general population was 1%-to-5%.[27][28] Among FMS patients, based on studies of thyroid function test results, the reported incidence of primary hypothyroidism was 10%-to-24%.[20][23][24][29][32]

My research group studied the incidence of central hypothyroidism among FMS patients using thyroid function test results and the dynamic TRH-stimulation test. Results were consistent with central hypothyroidism in 44% of patients.[21] This percentage was 250,000 times that in the general population.

In 1990, Forslind published a study[32] that casts a dark shadow of doubt on the existence of *primary* FMS—that is, FMS as a distinct disorder not underlain by another medical disorder. He and his colleagues examined 21 of 25 consecutive patients 5 years after they had received the diagnosis of primary FMS at a tertiary-care day-ward for patients with pain syndromes. The researchers concluded that only 15 of the 21 patients still met the criteria for FMS. However, *all* patients had developed either psychiatric disturbances or thyroid dysfunction. Among the 4 patients the researchers did not examine, two had developed neurological diseases, one had developed rheumatoid arthritis, and one other was hypothyroid. "Thus," the researchers wrote, "after 5 years no patient fulfilled the criteria for primary fibromyalgia." Hypothyroidism was the disorder most common among the patients.

In 1988, Carette and Lefrançois examined 100 patients for FMS (then termed "fibrositis") who, according to thyroid function test results, had subclinical or primary hypothyroidism.[200] Only 19 of the patients reported having joint and/or muscle pain with stiffness. The researchers did not diagnose all 19 patients as having FMS, however, because an essential criterion for the diagnosis was abnormal tenderness.

When Carette and Lefrançois examined the patients for tender points, only 5 of the 19 patients had 7 or more abnormally tender points. Requiring that patients have pain, stiffness, and tenderness to qualify for a diagnosis of FMS, Carette and Lefrancois wrote that only 5% of the 100 patients met the criteria for FMS.

The researchers then treated the 19 patients with muscle and/or joint pain with "thyroid hormone replacement." The symptoms of 10 of the 19 patients improved, including 3 of the 5 patients the researchers had diagnosed as having FMS. However, the researchers reported "no significant changes in tender points." They concluded, "Our data indicate that fibrositis is uncommon in patients with primary hypothyroidism despite the frequent occurrence of symptoms suggestive of this syndrome."[200]

Some FMS researchers I have communicated with have unfortunately falsely concluded that the Carette and Lefrancois study shows that hypothyroidism cannot be the main underlying mechanism of FMS. This clear-cut illogical conclusion is important to the erroneous belief that FMS and inadequate thyroid hormone regulation are unrelated.

The appropriate interpretation of the Carette and Lefrancois study result is the following. As this review demonstrates, a substantial published research literature shows a relationship between FMS and too little thyroid hormone regulation of cell function. In view of this, the pain and tenderness that rheumatology-paradigm FMS researchers consider the hallmarks of FMS plausibly combine to be one of *many* clinical phenotypes of hypothyroidism.

Thus, if we are for the moment to accept the criteria Carette and Lefrançois' used to diagnose FMS, the researchers would have more properly concluded: "Among our sample of 100 hypothyroid patients, only 5% met the criteria for fibrositis; this raises the possibility that fibrositis is a rare clinical phenotypic expression of hypothyroidism."

Logically, it is perfectly clear that this study did not rule out hypothyroidism as the main underlying mechanism of the 5 patients they diagnosed as having FMS. Instead, that 3 of the 5 patients improved with thyroid hormone replacement points toward hypothyroidism as the underlying mechanism of their FMS.

More importantly, it is highly probable that the "thyroid hormone replacement" the authors referred to was T_4-replacement. I say this because I know that in their Canadian province, T_4-replacement is typically autocratically imposed on hypothyroid patients. The importance of the use of T_4-replacement with these patients is that several studies show that many hypothyroid patients continue to suffer from hypothyroid symptoms despite their use of T_4-replacement.[196][197][198][201][202][203][204][205]

In a large community study, for example, close to 50% of patients on T_4-replacement continued to suffer from hypothyroid symptoms.[201] (For a critique of these studies, see Lowe.[199]) Had Carette and Lefrançois used a more effective approach to thyroid hormone therapy, it is highly likely (in view of the clinical trials cited below) that all 5 of their patients would have fully recovered, and they would no longer have had tender points.

Soy et al.[206] found that among patients with autoimmune thyroid disease, 62% had what they termed "rheumatic" conditions. Among patients with these conditions, the highest percentage (31%) met the criteria for FMS, which the authors falsely presumed to be a rheumatic disorder.

As with the Carette and Lefrançois study,[200] a reasonable conclusion from the finding of Soy et al. would be: "The clinical phenotypic expression termed 'FMS' is clearly not the clinical outcome of *all* patients with autoimmune thyroid disease." This conclusion does *not* rule out autoimmune-induced hypothyroidism as the main underlying mechanism of many patients' FMS.

Reports of studies conducted to determine whether there is a relationship between FMS and thyroid disease must be read carefully; otherwise, one might easily miss the indications of the relationship. Consider, for example, a 1993 study by Shiroky et al.[24] The researchers tested for the incidence of thyroid dysfunction among rheumatoid arthritis patients compared to patients with osteoarthritis and others with FMS. Shiroky et al. reported that 30% of women with rheumatoid arthritis had thyroid dysfunction. They noted that this percentage was three times the incidence of thyroid dysfunction among FMS patients. As I wrote above, based on the upper limit of the TSH at that time, researchers considered 1%-to-5% of the population at large to be hypothyroid. Considering Shiroky's statement, compared to the 30% of rheumatoid arthritis patients who were hypothyroid, 10% of FMS patients were hypothyroid. At that time, this percentage was significantly higher than the incidence in the general population.[24]

Objectively Verified Abnormalities Among FMS Patients

According to a group of French medical authors, "Fibromyalgia is a syndrome characterized by chronic musculoskeletal pain and fatigue *without biological detectable disturbances*."[207] (Italics mine.) This italicized statement is blatantly false; it suggests to me that the authors did not comply with the scientific responsibility of reviewing the relevant research literature before publishing statements on a scientific issue. For a journal's reviewers to fail to identify and prevent publication of such patently false statements reflects poorly on the journal. What is more, in my view, publication of such false information is a disservice from both the authors and the journal to clinicians who depend on the journal for scientifically accurate information.

Contrary to the false statement by these authors, Table 2 shows the objective abnormalities identified among FMS patients. These abnormalities have been documented through more than thirty years of research.

Hypotheses abound concerning the mechanism of FMS symptoms and some of these objective abnormalities. However, only a few such hypotheses have any scientifically credible backing. Of the hypotheses supported by some plausible evidence, none (except the inadequate thyroid hormone regulation theory) account for more than a few of the objectively verified abnormalities.

In stark contrast, the inadequate thyroid hormone regulation hypothesis (specifically, that too little thyroid hormone regulation is the main underlying mechanism of most patients' FMS) credibly accounts for at least 40 objectively verified abnormalities of FMS. As I documented in *The Metabolic Treatment of Fibromyalgia*, studies show that these same abnormalities also occur in a subset of patients with hypothyroidism or peripheral thyroid hormone resistance.[1,p.71(Table1.1.1),pp.341-766]

In Table 2 (40 objectively verified abnormalities in FMS), the cited studies show that each abnormality identified in FMS patients has also been identified in patients with hypothyroidism, peripheral thyroid hormone resistance, or both.

Table 2. Same objectively verified abnormalities in fibromyalgia (FM) as compared to hypothyroidism (HO) or peripheral resistance to thyroid hormone (PRTH).

ABNORMALITIES	FM	HO or PRTH
Histological		
↑ Hyaluronic acid	34,35	36
↑ Ground substance proteoglycans	11,12,37-39	40-43
↓ Collagen	44,45	46,47
↓ Pyridinoline	48,49	50,51
↓ Procollagen III	52-54	36,55,56
↓ Hydroxyproline	44,45,48,49	47,50,57,58
↑ Mast cells	37,38,59	46,60-64
CSF		
↑ Substance P	65-68	69-72
↓ Dopamine (homovanillic acid)	73	74,75
↓ Tissue norepinephrine	73	76-78
↓ Urinary 5-hydroxyindole acetic acid	79	80
↓ Brain 5-hydroxytryptophan	73,81	82
↑ Nerve growth factor	83	84,85
Molecular		
↑ α-Adrenoceptors	86,87	88-95
Mitochondria		
Ragged red fibers	96,97	98,99
↓ Cytochrome-c-oxidase	100	98,99
Physiological		
↓ Basal body temperature	183,184	192-195
↓ Resting metabolic rate	183,184	57,183,184
Exercise intolerance	101-104	105-108
↓ Muscle relaxation time	109	110
Blunted cortisol response to ACTH	111,112	113
Orthostatic hypotension	114,115	116
Joint hypermobility	117,118	119
↓ Brain blood flow	120-122	123
↓ Peripheral blood flow	124-126	127
Blunted sympathetic and end-organ response to stress	101,115,128-131	132-135
Excess urination	136,137	138,139
↓ Delta-wave and nonrestorative sleep	140,141	138,142-144
High-energy phosphates		
↓ ATP	145	146-149
↑ Phosphodiesters	150-152	153
↑ Inorganic phosphate (Pi)	151	153,154
↓ Phosphocreatine (PCr)	145	146
↓ PCr/Pi ratio	145	154,155
Carbohydrate metabolism		
↑ Pyruvate	156-158	105,156,159
↓ LDH	150,156	150,156
↓ Intracellular pH	150	153,154
↓ Skeletal muscle glucose use	160	161-163
Endocrine		
↓ HPA axis function	131,164	165,166
↓ GH and IGF-1	167-169	170,171
↑ Hypothyroidism	20-26	NA
↑ Hypothyroidism	20-26	n/a

Could the 40 abnormalities occur in all three disorders if the disorders did not have the same underlying mechanism? That is definitely within the realm of possibility. On the other hand, the mechanism could be the same, and I argue that logical analysis dictates that this conclusion is true—in the sense of "scientific truth," which, of course, is never conclusive.[217][218]

In my research team's efforts to refute the inadequate thyroid hormone regulation hypothesis, we conducted and published two studies in 2006. In each of these studies we measured the resting metabolic rates and basal body temperatures of FMS patients and compared them to healthy matched controls.

These studies came close to being the most vigorous challenges possible to the inadequate thyroid hormone regulation etiological hypothesis. Had our conjecture that FMS is mainly underlain by too little thyroid hormone regulation been refuted by these studies, the hypothesis would have been conclusively refuted and essentially demolished. However, the studies failed to refute the inadequate thyroid hormone hypothesis. To use an inductivist term, the outcome of the studies "supports" the inadequate thyroid hormone regulation hypothesis.

Because the studies failed to disprove the inadequate thyroid hormone regulation hypothesis, I describe the study results in the two sections below. Statistical analyses show that the differences between patients and controls were highly significant, both for basal temperatures and resting metabolic rates. Compared to matched healthy controls, women with FMS had significantly lower resting metabolic rates and basal body temperatures—*objective findings most consistent with too little thyroid hormone regulation of cell function in these FMS patients*. In each of the studies we ruled out any likely cause of patients' low resting metabolic rates and low basal body temperatures other than inadequate thyroid hormone regulation. *It is especially important to emphasize that in both studies, patients and controls were matched for level of physical activity, which rules out low physical fitness as the cause of the patients' lower mean metabolic rates and temperatures.*

Low resting metabolic rates of FMS patients. In the first study, patients' mean resting metabolic rate was 29% below their predicted rate (that which is considered normal) based on sex, age, height, and weight. The mean of the healthy control subjects' metabolic rates was only 8% below their predicted rates. (The "reasonable reference range" for resting metabolic rate is generally accepted as 10% below or above the predicted rate.)

In the second study, the mean resting metabolic rate for patients was 30% below the predicted rate. The mean metabolic rate of healthy controls was, again, 8% below the predicted rate.

Low basal body temperatures of FMS patients. In the first study, patients' average basal temperature was 96.95˚F. The average for healthy women was 97.54˚F. In the second study, the average temperature of patients was 96.38˚F. The average for healthy controls was 97.54˚F. Statistically, the patients' temperatures in both studies were significantly lower than those of controls.

Clinical Trials with Thyroid Hormone Therapy

Most FMS patients and their cooperative doctors want to know mainly one thing: Do we have an effective treatment for FMS? The answer is yes, although rheumatology-paradigm FMS researchers have *totally* ignored what Garrison and Breeding explained in *Medical Hypotheses* as "experimentally proven treatments."[208]

Patients have recovered from their FMS symptoms in two types of studies conducted by my research team and several others: open[172][173][174][175][176][190][191] and blinded[177][178][179][180][181] clinical trials. In 2002, Peter Warmingham commented on some of these studies in an article titled "Fibromyalgia Has Been Solved."[33] These are the only studies (those involving the use of thyroid hormone) in which patients have largely or fully recovered from FMS symptoms.

All these trials have included the use of thyroid hormone therapies *other than T_4-replacement*. I italicize the last phrase for an important reason: as I explained above [see "Studies of Thyroid Test Results"], T_4-replacement is ineffective for possibly 50% of hypothyroid patients who use it. As Garrison and Breeding noted after helping hundreds of thyroid hormone resistant FMS patients to recover with thyroid hormone, treatment usually involves supraphysiologic doses of T_3.[208] As my research team and others have found through at least two decades of clinical experience, a small percentage of hypothyroid FMS patients recover with T_4 alone. But few of them recover with T_4-replacement;

most must use TSH-suppressive dosages of T_4. For most patients to fully recover, however, they must use either combined T_4/T_3 therapy (with a 4:1 ratio of T_4-to-T_3) or T_3 alone.

A follow-up study by my research team showed the long-term effectiveness of treatment with thyroid hormone therapy other than T_4-replacement. In that study, we evaluated patients 1-to-5 years after they had undergone treatment with thyroid hormone therapy (combined with synergistic lifestyle practices). *It is important to note that most patients used thyroid hormone dosages larger than those used in T_4-replacement, in which patients use T_4 dosages that keep their TSH levels within the reference range; instead, safe and effective dosages were typically ones that kept patients' TSH levels below the lower end of the reference range*. We compared these patients to matched controls—patients we had evaluated earlier but who did not undergo treatment. Compared to the matched controls, the treated patients had statistically significantly improved. Moreover, their improvement lasted through the 1-to-5 year span, depending on the time of follow-up since they began treatment.[182]

In 1993, pediatricians at the Pediatric Rheumatology Center in Philadelphia described 5 children who had what they considered varied "rheumatic" conditions, including FMS and joint pain. They wrote, "*All musculoskeletal symptoms improved after thyroid replacement therapy.* We conclude that rheumatic manifestations of hypothyroidism can be as varied in children as in adults."[191] (Italics mine.)

Summary

Is it likely that too little thyroid hormone regulation of cell function is the main cause of most patients' FMS? I believe the line of evidence I have presented here sufficiently answers that question.

I fully anticipate, however, that rheumatology-paradigm FMS researchers will—as they have in the past—(1) marginalize any possible role of too little thyroid hormone regulation in FMS, (2) ignore the factual existence of thyroid hormone resistance, and (3) state or imply that hypothyroidism merely mimics FMS and should be differentiated from it by measuring patients' TSH levels.

For rheumatology-paradigm FMS researchers to disagree with the inadequate thyroid hormone regulation hypothesis of the etiology of FMS is respectable scientific conduct. However, to ignore the evidence upon which we base this conclusion is (to be euphemistic) not respectable scientific conduct. On behalf of FMS patients, I hope that these researchers finally open-mindedly consider the evidence I have assembled here, and acknowledge through their future publications that they can no longer simply ignore the evidence as though it did not exist.

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Thyroid Science

A journal dedicated to truth in thyroid science and clinical practice

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Submitted Letters about Dr. Rowsemitt's and Dr. Najarian's two papers

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Letters about the hypothesis paper and case reports by Thomas Najarian, MD and Carol N. Rowsemitt, PhD, RN, FNP

To submit a letter through *Thyroid Science* to an editor or to authors (as here to Dr. Najarian and Dr. Rowsemitt), if time allows you, please read our guidelines for submitting letters. We welcome you to submit your letter directly to an editor at Editor@thyroidscience.com. Otherwise, look for the author(s) email address(es) on either the abstract page or the formal pdf file of the author(s) full paper. Note that your letters may be edited or shortened simply for readability before we print it.

Please also note something else: Most authors of letters unfortunately choose to submit the letters to *Thyroid Science* as written "anonymously." That means, of course, that despite the value of the person's comments, the writer declines to submit his or her name. Both patients, physicians, and researchers are among those who choose to write anonymously. If you chose to do this, please accept our apologies for still publishing in what my brilliant mentor Robert S. Mendelsohn, MD described in the late 1980s as "the dark ages of medicine."

Were Dr. Mendelsohn still with us, he would clearly see that we have not advanced a jot from the darkness; in fact, we have sunken further into the dark vat where expressing what we have learned to be true is likely to bring upon us verbal abuse, other punishments, pain, and banishment from our commitment to do out best to relieve human suffering.

But alas! Despite suppression, freedom prevails in varieties of sectors today. We hope you will avail yourself here at *Thyroid Science* as one of those sectors. We are grateful for any insights and opinions you share with our authors, subscribers, and editors—disregarding whether you chose to write anonymously or not.

John C Lowe

Editor-in-Chief

Subject: Euthyroid patients: Many are harmed by thyroxine therapy
Date: June 20, 2010
From: Author prefers anonymity
To: editor@thyroidscience.com

June 20, 2010
Question: I am a general practitioner in the UK. Many of my patients have told me that they recovered from their hypothyroid symptoms after they found a private doctor who treated them with thyroxine despite their normal TSH levels. These patients had been denied thyroxine treatment by doctors within the National Health Service because of their normal TSH levels. So many patients have told me this that I have developed reservations about ruling out hypothyroidism and the need for thyroxine therapy based on a normal TSH test.

Many more of my patients with normal TSH levels ask me to prescribe thyroxine or Armour Thyroid. I am hesitant to comply because of the Royal College of Physicians' statement about adverse effects from unnecessary thyroid hormone therapy. May I have your point of view on the potential for adverse effects from thyroxine treatment when patients do not actually need it?

Dr. Lowe: I'm familiar with the statement you refer to by the Royal College of Physicians. Specifically it is: *". . . some patients are inappropriately diagnosed as being hypothyroid (often outside the NHS) and are started on thyroxine or other thyroid hormones which will not only cause them possible harm . . ."* (Italics and bold mine.)

Like too many other statements or implications by the Royal College of Physicians, when applied to the general population, this one is patently false.

Unless you're a geriatric specialist whose patients are among the most fragile of human beings, even if they don't need supplemental thyroid hormone, a trial of thyroid hormone therapy is harmless. If the hormone doesn't help them, you can wean them off it and then have them stop it altogether. No harm done!

Proof of this is in the history of FDA-guided studies of the potency and stability of T4. To test T4 for potency and stability, researchers—using FDA test guidance!—have traditionally used volunteers who were "euthyroid," meaning, of course, that they subjects had normal thyroid function test results. Moreover, FDA test guidance has allowed researchers to use euthyroid volunteers to test higher-than-physiological (supraphysiologic) doses of T4.[1,p.109]

I ask the Royal College of Physicians: If T4 were likely to harm *euthyroid* volunteers, why would FDA-test guidance allow researchers to use them for the testing? And why would institutional review boards approve the studies as not potentially harmful to the volunteers?

The answer is simple, of course: A trial of thyroid hormone therapy—even for people with perfectly normal thyroid function—is harmless, even when they use supraphysiologic doses.

Only recently have researchers suggested that rather than testing euthyroid volunteers, they would best use thyroidectomized patients. But the researchers' reason for this suggestion has nothing whatever to do with any harm ever done to euthyroid volunteers in the studies. The testing hasn't harmed the euthyroid volunteers, nor will a trial of thyroid hormone therapy harm practically any of your euthyroid patients except possibly the most severely fragile of them. But, then, a cup of coffee is just as likely to harm those fragile folks.

I just don't understand something: How does the Royal College of Physicians (as with this particular issue) and the British Thyroid Association make scientifically false statements and stand by them in the face of proof that they are false, yet receive no official reprimands from regulatory authorities in the UK? To me, their false statements are an affront to the noble tradition of science, and the organizations sticking by their false statements in the face of refuting evidence reduces the statements to examples of pseudoscience.

At any rate, I hope this reply is helpful to you in providing your patients with harmless trials of thyroid hormone therapy, whether they truly need it or not.

Reference

1. Royal College of Physicians. The diagnosis and management of primary hypothyroidism. 2008.

Subject: TSH is Not the Answer: Drs. Rowsemitt & Najarian
From: Writer prefers to stay anonymous
Date: Tue, July 26, 2011 9:41 am
To: editor@thyroidscience.com

Dear Dr. Lowe,

I'm glad that there are researchers and doctors that continue to work on Hypothyroidism. Over the years, I have continued to follow your website (I have your first book). You might be interested in my experience with TSH and the thyroid hormone.

I was diagnosed with Hashimoto's Disease in 1984, but did not take thyroid hormone until 1999 when I went from doctor to doctor for almost 2 years to find out what "disease" I might have. I had terrible symptoms of pain in my legs, numbness, not being able to think clearly, and generally not being able to walk without a cane. I was 51 and done with menopause, but doctors said that anti-depressants would help my "menopause symptoms," I threw them out because I wanted to get rid of the pain, not cover it up in "la la land."

After I was at least diagnosed with fibromyalgia, I found another doctor who prescribed Armour Thyroid, initially in tiny doses. (Synthroid did nothing for me. My TSH was 22.) This went on for months with the doctor increasing the dosage up to average. I still had symptoms that prevented me from working for 5 years. I lost a lucrative career and most of my life.

My symptoms would not subside (fibromyalgia, pain, could not get up from a sitting position, etc.). One day, I was sick of living with the pain and weakness. I decided to increase my dosage of Armour Thyroid to see if the excruciating pain in my legs would lessen. I honestly didn't care if I got a heart attack from it. I wrote a will before taking the dose. To my amazement and relief, I did not die, nor did my heart beat faster. The pain in my legs lessened. I continued increasing the dosage weekly until I felt o.k., not great, but able to function.

I was able to get a job in 2004 as a teacher, which keeps me very active during the day. I have been taking the dosage of 450 to 540 mg. of Armour Thyroid for 8 years. I am 62 years old, my blood pressure after medication is 120/76 and my heart rate continues to be normal. Even my Endocrinologist is surprised...he constantly tells me to take less medication, (He won't even prescribe the dose I'm taking . . . he writes "Take as Directed."

Finally, I have my life back. Thank you for your work.

Sincerely
An anonymous author

Subject: TSH is Not the Answer: Drs. Rowsemitt & Najarian
From: Best keep low profile because of you-know-who!
Date: Tue, July 26, 2011 10:08 am
To: editor@thyroidscience.com

Hello Dr. Lowe,

My GP has decided to slightly lower my T3 prescription from 15 mcg-to-10 mcg.

I have noticed that my religiously consistent exercise and diet regime has slightly affected my weight. He decided to do this as my T3 reading was heading for the high range. He thought I was slightly overdosing. In spite of this, I feel I need to be on 15 mcg so I'll print out this article for him, although I wish I had Dr. Rowsemitte's and Dr. Najarian's wisdom to work with.

Weight loss is difficult enough. As a hypothyroid patient (and 5 years post menopause), anyway, and If I had been exercising and dieting like this in my 20s and 30s I would probably be underweight. As it is, I am only just on the right side of the body mass index (high) for my height.

Regards and thanks for the articles by Dr. Rowsemitt and Dr. Nagarian.

Self protection through silence . . . C:

(Rather than responding directly, this writer instead linked to Dr. Lowe's introduction to and defense of Drs. Rowsemitt & Najarian's two published papers.)

Subject: TSH is Not the Answer: Drs. Rowsemitt & Najarian
From: I choose to abstain from divulging my name, for obvious reasons
Date: Fri, September 30, 2011 9:08 pm
To: editor@thyroidscience.com

Disagree with these two humane and brilliant doctors? Too another look and alternate opinion.

Subject: TSH is Indeed ***Not*** the Answer: Praise for Dr. Rowsemitt & Dr. Najarian
From: A physician who lives in fear of quack endocrinologists.
Date: Monday, Date: Aug. 18, 2011 8:30 AM
To: Dr. John C. Lowe, LLC <editor@thyroidscience.com>

Dr. Lowe: I sit in my medical office this morning shuttering the deceit I am forced to express to the quack endocrinologists who practice in my medical complex. If they were aware of how I rescue the patients they keep sick with their pseudo-scientific medical practices, they would arrange to have my license to practice medicine revoked. I have seen it happen.

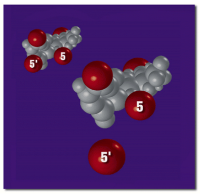
Then I read this awe inspiring two papers in Thyroid Science by your champion of doctors and writers, Dr. Najarian and Dr. Rowsemitt. I wonder at how they have been able to survive to practice medicine in a world dominated by medical pseudo-science and quackery. I wish I knew the magic they exercise, while those of us, such as myself, with student loans over our heads, mortgages, wives and college children hide in the shame that endocrinologists have forced us into.

Bless you, Dr. Lowe, for giving Dr. Rowsemitt and Dr. Najarian—*glittering heroes of scientific truth!*—an open forum to expresses what God and science have allowed them to see and express.

Subject: TSH is Not the Answer: Drs. Rowsemitt & Najarian
Date: Monday, July 28, 2011 10:44 PM
To: Dr. John C. Lowe, LLC <editor@thyroidscience.com>

Dr. Lowe: Having known and worked with Robert S. Mendelsohn, MD, I believe he was right about so much that was so dreadfully wrong with mainstream medicine in his days. But of late, having studied the bravery and knowledge of extraordinary doctors such as Drs. Carol Rowsemitt and Thomas Najarian, including you and others like you, I believe much has taken a turn for the better since the time of our beloved Dr. Mendelsohn. Praise you all, and may the Lord bear with you all until sanity finally overcomes mainstream medicine and completely wins out.

As I still work in mainstream medicine, thank you for keeping my name private.



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Letters Related to Dr. Lowe's Rebuttal to the British Thyroid Association

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| General Letters | Dr. Allahabadia's Reply |

Subject: Reply to rebuttal to the BTA's opinions
From: editor@thyroidscience.com
Date: Mon, March 15, 2010 9:01 am
To: Amit.Allahabadia@sth.nhs.uk
Secretary, British Thyroid Association

Dear Dr. Allahabadia,

I initially wrote to you in March 16, 2009—one year ago—asking that the British Thyroid Association (BTA) respond to my rebuttal <http://www.thyroidscience.com/Criticism/lowe.3.16.09/bta.rebuttal.htm> to its opinions on levothyroxine, T4/T3 combination therapy, and desiccated thyroid. You wrote back to me in August 2009 saying that the BTA would respond “in due course.”

I consider that due course has long since passed. If the BTA does not enter discourse over its opinions, then its opinions can justifiably be considered authoritative and dogmatic rather than rational and scientifically-based.

I request once more that the BTA reply to the various points in my rebuttal. Considering how long it has been since I initially wrote to the BTA, a prompt response from the BTA is imperative. The reason is that many practitioners are likely to accept without question that the BTA’s opinions are scientifically accurate. Because some of the BTA’s opinions, expressed in its Executive Committee’s document, are patently false, which I documented in my rebuttal, some of these practitioners may make decisions on behalf of hypothyroid patients that adversely affect the health and well-fare of hypothyroid patients.

It is in the interest of quality care for hypothyroid patients, and in the spirit of traditional scientific values, that I ask again that the BTA to reply to my rebuttal.

Sincerely,
Dr. John C. Lowe
Editor-in-Chief
Thyroid Science

Subject: RE: Request for reply from the British Thyroid Association
From: Amit.Allahabadia@sth.nhs.uk
Date: Tue, April 7, 2009 4:22 am
To: editor@thyroidscience.com

Dear Dr Lowe

Thank you for e-mail. The Executive Committee of the British Thyroid Association will consider your comments in due course in consultation with The Royal College of Physicians.

Best wishes
Dr Amit Allahabadia
Secretary of The British Thyroid Association

Subject: Request for reply from the British Thyroid Association
From: editor@thyroidscience.com
Date: Tue, April 7, 2009 4:11 am
To: Amit.Allahabadia@sth.nhs.uk

To: Dr Amit Allahabadia
Secretary: British Thyroid Association
Sheffield Teaching Hospitals, Sheffield

Dear Dr. Allahabadia,

Below is an email I send to you and the British Thyroid Association (BTA) on March 16, 2009. In the email, I invited a response from the BTA to be published without censorship at *Thyroid Science* in the spirit of scientific discourse. I have not received a response from you or from any other representative of the BTA. I will be grateful if you or another representative will give us the courtesy of letting us know, at minimum, that you received my email, but hopefully also letting us know whether we can expect a response from the BTA. Thank you for taking the time to reply.

For your convenience, below is the webpage address to my rebuttal to the BTA's document on natural desiccated thyroid and synthetic T4/T3 therapies:

http://www.thyroidscience.com/Criticism/lowe.3.16.09/bta.rebuttal.htm

Best regards,
Dr. John C. Lowe
Board Certified: American Academy of Pain Management
Director of Research: Fibromyalgia Research Foundation
Editor-in-Chief: ThyroidScience.com
(603) 391-6061, www.drlowe.com
drlowe@drlowe.com Tammy@drlowe.com
drlowe@FibromyalgiaResearch.org

Subject: Rebuttal to British Thyroid Association's document on natural desiccated thyroid
From: editor@thyroidscience.com
Date: Mon, March 16, 2009 2:12 pm
To: Amit.Allahabadia@sth.nhs.uk

To: Dr Amit Allahabadia
Secretary: British Thyroid Association
Sheffield Teaching Hospitals, Sheffield

Dear Dr. Allahabadia,

I have included below a link to a rebuttal I have written to the British Thyroid Association (BTA). The rebuttal concerns the BTA Executive Committee's 2007 document on natural desiccated thyroid and levothyroxine. After having critically analyzed the Committee's document, I believe it constitutes a gross disservice to patients and clinicians who might read and be mislead by its unbalanced presentation of evidence and the false statements it contains. I feel it is proper to let the BTA know about my rebuttal so that its officials can respond, hopefully by correcting the misinformation the 2007 document contains. We at *Thyroid Science*, of course, will be happy to publish any statement the BTA decide to make in response to the rebuttal.

http://www.thyroidscience.com/Criticism/lowe.3.16.09/bta.rebuttal.htm

All best wishes,

Sincerely,
Dr. John C. Lowe
Board Certified: American Academy of Pain Management
Director of Research: Fibromyalgia Research Foundation
Editor-in-Chief: ThyroidScience.com
(603) 391-6061, www.drlowe.com
drlowe@drlowe.com Tammy@drlowe.com
drlowe@FibromyalgiaResearch.org

Thyroid Science

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To submit a letter to an editor or author through *Thyroid Science*, please read our guidelines for submitting letters. Submit your letter to Editor@thyroidscience.com. Letters may be edited and shortened. *Thank you*.

| Letters related to Dr. Lowe's rebuttal to British Thyroid Association |
| Readers responses to Dr. Najarian and Dr. Rowsemitt's two papers |

Subject: Are euthyroid patients harmed by thyroxine therapy
Date: June 20, 2010
From: Author prefers anonymity
To: editor@thyroidscience.com

June 20, 2010
Question: I am a general practitioner in the UK. Many of my patients have told me that they recovered from their hypothyroid symptoms after they found a private doctor who treated them with thyroxine despite their normal TSH levels. These patients had been denied thyroxine treatment by doctors within the National Health Service because of their normal TSH levels. So many patients have told me this that I have developed reservations about ruling out hypothyroidism and the need for thyroxine therapy based on a normal TSH test.

Many more of my patients with normal TSH levels ask me to prescribe thyroxine or Armour Thyroid. I am hesitant to comply because of the Royal College of Physicians' statement about adverse effects from unnecessary thyroid hormone therapy. May I have your point of view on the potential for adverse effects from thyroxine treatment when patients do not actually need it?

Dr. Lowe: I'm familiar with the statement you refer to by the Royal College of Physicians. Specifically it is: ". . . some patients are inappropriately diagnosed as being hypothyroid (often outside the NHS) and are started on thyroxine or other thyroid hormones ***which will not only cause them possible harm*** . . ." (Italics and bold mine.)

Like too many other statements or implications by the Royal College of Physicians, when applied to the general population, this one is *patently false.*

Unless you're a geriatric specialist whose patients are among the most fragile of human beings, even if they don't need supplemental thyroid hormone, a trial of thyroid hormone therapy is harmless. If the hormone doesn't help them, you can wean them off it and then have them stop it altogether. *No harm done!*

Proof of this is in the history of FDA-guided studies of the potency and stability of T4. To test T4 for potency and stability, researchers—*using FDA test guidance!*—have *traditionally* used volunteers who were "euthyroid," meaning, of course, that they subjects had normal thyroid function test results. Moreover, FDA test guidance has allowed researchers to use euthyroid volunteers to test higher-than-physiological (supraphysiologic) doses of T4.[1,p.109]

I ask the Royal College of Physicians: If it were likely to harm euthyroid volunteers, why would FDA-test guidance allow researchers to use them for the testing? And why would institutional review boards approve the studies as *not potentially harmful* to the volunteers?

The answer is simple, of course: A trial of thyroid hormone therapy—even for people with perfectly normal thyroid function—is *harmless*, even when they use *supraphysiologic* doses.

Only recently have researchers suggested that rather than testing euthyroid volunteers, they would best use thyroidectomized patients. But the researchers' reason for this suggestion has *nothing whatever* to do with any harm ever done to euthyroid volunteers in the studies. The testing hasn't harmed the euthyroid volunteers, nor will a trial of thyroid hormone therapy harm practically any of your euthyroid patients except possibly the most severely fragile of them. But, then, a cup of coffee is just as likely to harm those fragile folks.

I just don't understand something: How does the Royal College of Physicians (as with this particular issue) and the British Thyroid Association make scientifically false statements and stand by them in the face of proof that they are false, yet receive no official reprimands from regulatory authorities in the UK? To me, their false statements are an affront to the noble tradition of science, and the organizations sticking by their false statements in the face of refuting evidence reduces the statements to examples of pseudoscience.

At any rate, I hope this reply is helpful to you in providing your patients with harmless trials of thyroid hormone therapy, whether they truly need it or not.

Reference

1. Royal College of Physicians. The diagnosis and management of primary hypothyroidism. 2008.

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(This Q&A was published simultaneously at drlowe.com)

Letter to the Editor

Subject: Question about where to submit my paper
Date: June 12, 2010
From: Author prefers anonymity
To: editor@thyroidscience.com

June 12, 2010
Question: I have a hypothesis paper that I'm considering submitting to *Thyroid Science*. I'm hesitant, however, because there may be advantages to publishing in major medical journals, such as the *Journal of the American Medical Association*. Of course, I may have a harder time getting my paper accepted because of competition. What are your thoughts for people who are new to submitting papers to journals? Can I submit my paper both to *Thyroid Science* and another journal and go with which ever journal accept it?

Dr. Lowe: Many people have asked us this same question. Of course, we would like a chance to publish your paper if our reviewers believe it has merit in the field of thyroidology. However, if your paper may contribute to changing the current "T4 replacement paradigm" for hypothyroidism, we really don't care which journal first publishes it, as long as you get it published.

To some, that policy may seem self-sabotaging to *Thyroid Science,* but it really isn't. If we feel that a paper published elsewhere is important enough, we'll ask the author(s) to write a summary of the paper for our journal, possibly further articulating the thesis and providing more supporting evidence. And if the author won't cooperate, we may compose a paper based on the author(s)' that provides the important information for our readers.

In deciding where to submit your paper, you might keep in mind a few points I wrote to another potential author this morning. What I wrote to him is essentially the following.

Long ago, when I was being educated in research psychology (I think Galileo sat two rows in front of me), I took courses that dealt with the ethics of scientific conduct. We were taught that it's unethical to publish exactly the same paper in more than one journal, even if years have passed since the first publication. That policy is an old one, and it still applies. Because of this, you should submit your paper only to one journal at a time. If the first journal rejects your paper, then, and only then, submit it to the next one.

If you want to spread your hypothesis wider than one journal would allow, you can easily do that. First, publish your paper in one journal, and write as many other papers as you want for other journals. This is perfectly ethical as long as your other versions of your paper are indeed other versions; that is, in subsequent papers, you should express your hypothesis exactly as it was originally published, but *in different terms*. Expressing the same thoughts in different terms is ethical. In my view, in fact, if you feel that your hypothesis can lead to the relief of suffering of human beings, you have a humanitarian responsibility to publish it as many times as needed to accomplish that worthy end.

If you can get your paper accepted by a major traditional print journal, you'll have some important advantages. For example, you're likely to have more prestige in the eyes of the typical practicing conventional clinician, and your paper will be included in the traditional major indexing systems, such as Medline.

On the other hand, the print journal may fail to publish your paper in an open-access electronic version of the journal. If so, only those who subscribe to the print version of the journal are likely to read your full paper. As time passes, the only part of your paper that most interested people will have access to will be the abstract that is online. They can access your abstract through most search engines, such as Google and Yahoo.

Otherwise, if anyone is interested enough in arrange to get a copy of your full paper, he or she will have one of two options: First, he or she can buy a copy online from the closed-access journal. This can be expensive, and it can be prohibitive if one does a great deal of journal research. Second, he or she can travel to a medical library, track down your paper in a bound volume of all the papers published in that journal during the year, and photocopy it. This option is inconvenient for most people. This may account for me seeing in recent years fewer and fewer people in medical libraries copying journal papers.

Another downside of traditional print journals is something that frustrated many of us who used to publish in traditional print journals: the "publication lag." I know of some journals that had a lag of two years. This meant that by the time one's paper was published, it was more history than news. Because of the publication lag, I encourage you talk or write to an editor of the journal you decide to submit to. As whether in addition to publishing a print version, the journal will also rapidly publish an electronic version online.

Another important issue is whether the journal is available only to subscribers ("closed-access") or is "open-access." Open-access means that most publications in the journal are free to read without a subscription. Steadily more open-access journals are being published, and they are impacting traditional print journals. When I've inquired, medical librarians, who work where traditional print journals are stored, have told me, "open-access journals are killing us."

One advantage of electronic publishing, especially in open-access journals such as *Thyroid Science*, is that we have virtually no publication lag. We publish papers are rapidly compared to print journals. In addition, with open-access journals, anyone in the world with access to the Internet can find and read your paper using Google, Yahoo, or most any other search engines. One doesn't even need to use Medline, PubMed, or any of the other traditional indexing system. In fact, I believe these systems are on the verge of being obsolete. Most search engines such as Google also index the papers that formerly were indexed only in the traditional indexing systems. Plus, Internet search engines also indexe publications *not* included in PubMed.

If you publish in another journal for whatever advantage, we fully support you in it. And if you'll send us an advanced copy of your paper, after the other journal publishes it, we may ask you to summarize your hypothesis and elaborate on it in a second paper for *Thyroid Science*.

Best of luck in getting your hypothesis published, wherever you decide to submit your paper.

Letter to the Editor

Subject: What is prealbumin
Date: November 24, 2009
From: Author prefers anonymity
To: editor@thyroidscience.com

My doctor gave me my lab results yesterday. I know what most of the thyroid tests are, but I've never heard of one. It is the "prealbumin." Do you know what this is? My level was 0.20 g/L, and the range is listed as 0.18-to-0.39 g/L. Do you know what this result means?

Reply by Dr. John C. Lowe, Editor-in-Chief (November 24, 2009)

Dear Bob: We have a newer name for prealbumin, which is "transthyretin." Transthyretin is a protein that is important to thyroid hormone regulation of the brain. The protein transports thyroid hormone across the blood-brain barrier; that is, from the blood outside the brain to the blood inside brain. Transthyretin that transports thyroid hormone in the blood is produced in the liver, but transthyretin that transports thyroid hormone across the blood brain barrier is produced in a structure called the "choroid plexus" at the base of the brain.

When I say that the protein transports thyroid hormone across the blood-brain barrier, I mean that it transports both T4 and T3. This is important to understand. The reason is that many clinicians mistakenly think that transthyretin transports only T4 into the brain. Based on this mistaken belief, these clinicians also mistakenly believe that normal brain function depends on patients including T4 in their thyroid hormone therapy. This, however, is patently false. (Elsewhere, I extensively documented that transthyretin transports both T4 and T3 into the brain. I published one article in 2005 and the second in 2006.)

You wrote that your transthyretin level was 0.20 g/L (20 mg/dL). With a range of 0.18-to-0.39 g/L (18-to-39 mg/dL), your level is very low; it's in the lower 4th of the range.

Some diagnosticians would say this level means you're not producing an optimal amount of transthyretin; others would say that you're producing plenty. I don't think we have enough studies to tell us which of those diagnosticians are right and wrong.

What we can tell from your level is that you're producing the protein and your most likely getting thyroid hormone into your brain. We don't have tests commercially available that measure the amount of thyroid hormone that is bound to one's transthyretin. That piece of information would be valuable. The reason is that dioxins and PCBs can displace thyroid hormone from the protein. As a result, these chemical contaminants can ride into the brain on the protein. The more of the contaminants that ride the protein into the brain, the less T4 and T3 are likely to reach brain cells. Once inside the brain, dioxins and PCBs bind to T3 receptors on genes. The binding alters the pattern of codes that the genes send out to the work part of the cell for the production of proteins. I believe this phenomenon is responsible for some of the cognitive and mood problems of people contaminated with dioxins and PCBs, which toxicologists have told me is each of us. (I heavily documented the thyroid-disrupting effects of these pollutants in the "Environmental Contaminants" section in Chapter 2.4, "Thyroid Hormone Deficiency," of *The Metabolic Treatment of Fibromyalgia* [available in the publisher's E-Chapter section].)

I assume that you wrote to me about your transthyretin level from concern about your thyroid hormone status. However, some clinicians order the test to learn whether a patient is ingesting enough protein. Transthyretin is a "glycoprotein," which means it is a carbohydrate combined with a protein. Of all the proteins in the blood, it's transthyretin that is most useful in telling whether a person has a protein deficiency. The half life of the protein is about two days, so it's level in the blood changes quickly when someone markedly decreases or increases protein intake, digestion, and/or absorption.

You didn't say whether you ate little to no protein for several days before your blood was drawn to measure your transthyretin. If you ate little to none, that might account for your low-range transthyretin level. If that is the case, you should talk with your clinician about measuring your transthyretin level again after you eat 50-to-75 grams of protein each day for several days. Your tranthyretin level might then be higher. But keep in mind that inflammation and infection can also lower transthyretin level, and severe kidney disease and the use of glucocorticoid (such as prednisone or prednisolone) can raise your level. I hope this is helpful to you.

Letter to the Editor

Subject: Followup photo of goiter patient
From: Ned Fuller
Date: March 1, 2009 10:08 am
To: editor@thyroidscience.com

My mother has a goiter and it has been advised that she have it surgically reduced. I am a physician but have not had the opportunity to see the postsurgical appearance of the neck after a patient's goiter has been removed. My mother is concerned about the appearance, although she is also concerned about the appearance of the goiter. Are there any postsurgical photos of the patient whose goiter Drs. De Sousa, Dilip, Mervyn removed.

Editor's Reply (March 2, 2009)

Dear Dr. Roberts: We asked Dr. DeSousa if any photos were available of the patient whose goiter he and his colleagues reported removing. He was kind enough to send the postoperation photo to the right below. We also posted below the photo of the patient from the authors' case report before they removed the goiter; it is the photo to the left.

Dr. De Sousa wrote to us that the photo to the right is the patient after two weeks of convalescence. The scar had been painted with mercurochrome. We are grateful to Dr. De Sousa for providing *Thyroid Science* with the photos, and I hope the postop photo is helpful to you, Dr. Roberts.

Tracy Majors
Assistant Editor

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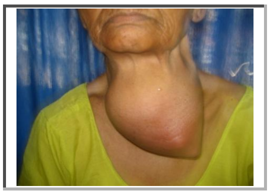

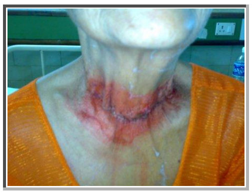

Letter to the Editor

Subject: Thanks to you!
From: Jacqueline Herrera
Date: Mon, December 8, 2008 9:32 pm
To: editor@thyroidscience.com

Dear Dr. Lowe: I'm so thankful I was told about ThyroidScience.com. I read the article on "Weight Gain and the TSH" and sent it to my three sisters who also suffer from hypothyroidism. I started the Armour Thyroid medication almost two weeks ago and feel so much better than the last 7 years of being on levothyroxine. I know this is a positive start in the right direction for me personally. I have 30 pounds to get rid of that I've gained in the last 7 years after two consecutive pregnancies in 2002 and 2003. Thank you for making this information available to the people (not just doctors) who are pro active about their health.

Jacqueline Herrera
Phoenix, Arizona

Editor's Reply (December 25, 2008)

Dear Jacqueline: Thanks so much for writing about feeling better on Armour Thyroid after gaining thirty pounds of weight while on levothyroxine. If you use a high enough dosage of Armour, I expect that you'll lose the 30 lbs you gained over the seven years that you used levothyroxine. This is especially likely if you have a wholesome diet and regularly exercise to tolerance.

Armour Thyroid, like Nature-Throid and Westhroid, is more effective than levothyroxine at reducing body fat. The reason is that these products contain T3. Some researchers say that T3 has a "lipolytic"—that is, a fat-decomposing —action in fat cells.[3] One way T3 reduces fat in the cells is by inhibiting an enzyme (cyclic-AMP phosphodiesterase) that slows down metabolism shortly after adrenaline and noradrenaline speeds it up.[1][3][8] By blocking this enzyme, T3 sustains the fat-decomposing effect of adrenaline and noradrenaline in fat cells.[1][2][8] Another way T3 reduces fat is by altering gene transcription for several compounds. When T3, acting through the relevant genes, increases fat cells' production of these compounds, the compounds augment adrenaline's and noradrenaline's fat-lowering effect in the cells.[10]

In addition to weight loss, you may get another benefit from the T3 in Armour: that is, a reduction of fat that probably accumulated in your arteries[3] while you were on T4 replacement. As Duntas wrote,[11] As Duntas noted in 2002, the composition and transport of blood fats "are seriously disturbed in thyroid diseases." Among patients with an high TSH and low thyroid hormone levels, cholesterol and LDL are typically high. Even when thyroid hormone levels are within the reference range but the TSH is high, patients on average have a slightly high total cholesterol, high LDL, and low HDL. These patients also have abnormalities of the linings of arteries, inflammation and fat accumulation in the aorta, and they are subject to have myocardial infarctions. They also have increased resistance to blood flow, weaker contractions of the heart muscle, and increase diastolic blood pressure. As Duntas pointed out, thyroid hormone therapy—*especially with TSH-suppressive dosages*—"usually leads to a considerable improvement in the lipid profile."

T3 reduces fat in artery linings in part by increasing the activity of an enzyme called "lipoprotein lipase."[4] Low activity of this enzyme leads to high blood fats, which is a risk factor for coronary heart disease.[7] Thyroid hormone increases the activity of the enzyme, and by doing so, it reduces blood fats.[4] Thyroid hormone also lowers LDL cholesterol by increasing the number of LDL receptors on liver cells.[11]

In my clinical experience, thyroid hormone therapy (with products that contain T3) is by far more effective than statin drugs in normalizing blood fats. I believe that if patients in general were allowed to use effective thyroid hormone therapy rather than T4 replacement, we could virtually eliminate the market for statin drugs. Then patients would be free from the potential adverse effects of statin drugs, such as chronic muscle pain and other pain syndromes, elevated liver enzymes, peripheral neuropathy, and muscle damage.[9]

Please let us know how you progress. I wish you the best for losing the weight you gained while on levothyroxine.

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Letter to the Editor

From: "Lars" <staff@bicom.se>
Date: Sun, November 16, 2008 2:06 am
To: Editor@thyroidscience.com

Has the paper below really been reviewed????

http://www.thyroidscience.com/studies/overbye.2007/overbye.metabolicfailure.fms.lowethesis.pdf

I do not question the Lowe thesis, but I believe that a poor paper to support it is in fact harming the cause—especially if the methods used are not backed up with known or accepted methods.

Kind regards
Lars Németh
Med Vänlig hälsning
+46 40 137 765

Editor's Reply

Dear Mr. Németh: Thank you for your email and your thoughts. Yes, indeed: Dr. Øverbye's paper was reviewed. Several of our peer reviewers read the paper, and each strongly recommended that we publish it. As one of the reviewers commented after critiquing Dr. Øverbye's manuscript, "This paper reports the type of cutting-edge, creative pilot research that we want to encourage."

You suggest that Dr. Øverbye's paper is "poor" because his methods were "not backed up with known or accepted methods." In conventional medicine, of course, creative research using innovative methods has traditionally been resoundingly discouraged. Recall the dictum, "Be not the first by whom the new is tried, nor the last to lay the old aside." We at *Thyroid Science* reject this progress-stifling, herd-mentality orientation. Instead, we encourage originative and progressive clinical methods and research. That orientation is exemplified by *Thyroid Science* publishing Dr. Øverbye's paper. As objectionable as this orientation may be to some people within conventional medicine, we steadfastly stand by it, as we believe this orientation is likely to bring help to millions of thyroid patients whom conventional medicine continues to fail.

Your assessment of Dr. Øverbye's study and his paper brings to mind similar notable occurrences. They involved Professor Linus Pauling, a two-time Nobel Prize winner ranked among the ten most fruitful scientists in history. Pauling was also fruitful in his scientific investigations in the field of nutrition. But editors of medical journals often censored him by rejecting or delaying publication of his manuscripts because the contents challenged conventional medical prejudices. (To read his description of the censorship by editors—including the editor of the *Journal of the American Medical Association*—read his chapter titled "Organized Medicine and the Vitamins" in his book for the public titled *How to Live Longer And Feel Better*.)

By contrast, after some resistance early in his career, chemistry journals accepted Pauling's thinking and methods that were clearly beyond the boundaries of "the box." Some editors accepted his manuscripts containing extremely innovative material without sending them to peer reviewers. As one editor noted, peer reviews were impossible in that Pauling had no peers. The chemistry profession got the benefit of Pauling's imaginative and innovative mind. But censorship of this scientific genius protected from refutation the presumptions and prejudices of the editors, commercial sponsors, and readers of some medical journals.

I'm not saying that Dr. Øverbye's paper is certain to have the gargantuan scientific importance of many of Pauling's papers (although I'm also not saying it won't). What I am saying is that *Thyroid Science* will not censor research simply because it involves thoughtful, fresh ideas, and innovative methods. As in Dr. Øverbye's case, we encourage researchers to use well-established technologies from other fields to make scientific advancements in the field of medicine. He has done this, and admirably so.

We appreciate you expressing your opinion and prompting us to explain why our reviewers and editors enthusiastically accepted Dr. Øverbye's paper for publication.

Best wishes,
Dr. John C. Lowe
Editor-in-Chief
Thyroid Science (Editor@ThyroidScience.com)

Letter to the Editor

Subject: Thyroid Weight Gain
From: June Hyslop <Scotland, UK>
Date: Sun, November 16, 2008 6:34 am
To: editor@thyroidscience.com

Dear Dr. Lowe: I am printing off a copy of your article "Weight Gain and the TSH: Prevention Writer's Good Deed." I will take it to my next appointment with my endocrinologist in the hope that he'll read it and adopt a less conservative approach to the management of my hypothyroidism. At my last visit he cut my thyroid medication because I was too near the top of the range for FT3 and FT4 (my TSH is suppressed already). It's now two months later and I have gained five pounds. As I was already overweight and have extreme difficulty losing any, this is a big setback for me. I'm also fatigued and have seen the return of other hypothyroid symptoms since the reduction in dose.

I feel there is a lack of understanding within the endocrinology community about how this affects patients physically and mentally, and I would like to see a more open-minded and individualized approach to patient management. Your efforts in this regard are greatly appreciated, and I look forward to receiving future issues of *Thyroid Science*.

June Hyslop
Scotland, UK

Editor's Reply

Dear June: Thank you for your email. Since we published the editorial on weight gain and the TSH, we've received many emails from hypothyroid patients expressing the same lament that you do. Over the years, I've heard so many patients express the same grief that I couldn't begin to count them. Your complaint about weight gain and those of many others, and the studies I cited in the editorial, make one point clear: basing hypothyroid patients' treatment on their TSH levels (or their thyroid hormone levels) is an egregious wrong imposed on the patients. Indeed, that approach is the very cause of many patients gaining weight that they can't lose despite regular exercise and a wholesome, nonfattening diet.

One way to rectify this wrong in medical care is exactly what you've said you'll do—put the evidence of its harm, shown in studies, before the eyes of endocrinologists and other practitioners. Patients must, of course, insist that the clinicians pay attention to the studies and rationally consider them. Of course, it's now legend that many endocrinologists rudely dismiss patients who bring to their attention scientific evidence that contradicts their beliefs. The patient who accepts the dismissal and finds a more scientifically-thinking clinician is fortunate; he or she is far more likely to receive safe and effective care.

According to case law in the U.S., clinicians have a professional responsibility to stay abreast of scientific evidence that bears on the opinions they give their patients. So for an endocrinologist to deny to a patient that weight gain is associated with in-range rising TSH levels is—by virtue of the available scientific evidence—a breach of professional responsibility. But this is a breech that many endocrinologists sidestep. They do so by deferring to the practice guidelines written by committees within their specialty. The practice guidelines dictate standards for the diagnosis and treatment of hypothyroidism both within the endocrinology specialty and, by extension, in other medical specialties. Largely under the sway of corporations' financial inducements, too many of the members of these committees ignore the scientific evidence that shows the potential harm from parts of their guidelines that favor corporate profits. (I heavily document these potential harms throughout *The Metabolic Treatment of Fibromyalgia*.) In essence, then, these committees nullify the practicing endocrinologists' responsibility to listen and learn when patients troubled by weight gain give them the scientific evidence that the gain is associated with TSH levels within the reference range.

This harmful system within the endocrinology specialty has alienated countless hypothyroid patients who now hold the specialty in contempt. I believe this is a good dynamic because of a phenomenon in the 20th century history of medicine in the U.S. That phenomenon was that major changes in medicine came about because enough patients demanded them and made them profitable. The patients sought out and paid clinicians who provided services they wanted. Many of those patients wanted the services because they, unlike the clinicians, knew of scientific evidence that the services could benefit them. This market demand was a major influence on the emergence of sports medicine, nutritional medicine, integrative medicine, and manual manipulation by medical practitioners. Scientific evidence favoring these methods had long existed. It received little-to-no attention by physicians, however, until patients made it profitable for them to provide the services warranted by the evidence.

Will the endocrinology specialty overall yield to mass patient demand? Not until that huge barricade of corporate money is ceases to wall off the minds of most endocrinologists from the scientific evidence. Removing that barricade will be a difficult task indeed in this world where corporatism overwhelmingly prevails.

Over the last several years, however, I've seen signs that a minority of endocrinologists have come around. If patients like you seek out and patronize those endocrinologists, their numbers are likely to grow. I encourage you, then, to put the editorial on weight gain and the TSH before your endocrinologist's eyes. (I recommend that you print the pdf version of the editorial, which you can download or print at no cost.) If you are rebuffed in your attempt to enlighten him, I hope you'll move on and find one within that minority of endocrinologists who'll give you better quality care by ignoring the levels of your TSH and thyroid hormones in deciding what dosage is best for you.

Yours sincerely,
Sincerely,
Dr. John C. Lowe
Editor-in-Chief
Thyroid Science (Editor@ThyroidScience.com)

Subject: Re: Doing better on Armour
From: Anonymous patient in Australia
Date: Wed, August 27, 2008 6:11 pm
To: editor@thyroidscience.com

Dear Editors: I bow down to you as I read everything you publish on thyroid. Please keep it up. After using thyroxine, I now use Armour and finally feel better.

Dear Reader: The next Q&A down from this one is a question from a physician and an answer to it by Dr. John C. Lowe, our Editor-in-Chief. As his answer indicates, we at *Thyroid Science* are aware of the superiority of desiccated thyroid products, such as Armour, Nature-Thyroid, and Westhroid, over thyroxine (T4) alone. You may find very interesting an article we will soon publish. It is a rebuttal by Dr. Lowe to the British Thyroid Association's denouncement of desiccated thyroid products. We will send an email notice to our subscribers when we publish the rebuttal. We appreciate you letting us know that you are doing better on desiccated thyroid.

Sincerely,
Tracy Majors
Assistant Editor
Thyroid Science (www.ThyroidScience.com)

Subject: **Safety Precautions for Thyroid Hormone Therapy**
From: Anonymous physician
Date: Thu, August 24, 2008 12:29 pm
To: Editor@thyroidscience.com

Dear Dr. Lowe: I am one of the many family physicians who has jumped off the ship of conventional medicine and onto that of natural medicine. I spent my first twenty years of practice disserving my thyroid patients by prescribing Synthroid only and changing their dosages by their TSH levels. It didn't take much experience for me to see that products like Nature-Thyroid work better than Synthroid with most patients, especially when I ignore their TSH (as you give evidence for doing in your critique of T4 vs T4/T3 studies) and go by their symptoms, temperature, Achilles reflex, and physical appearance. I read in your book *The Metabolic Treatment of Fibromyalgia* about the change in some patients' eyes and general appearance when they switch from T4 to desiccated thyroid or T3. When I use these meds correctly, they almost always seem to turn up the patient's rheostat, whereas usually Synthroid just left it turned off. I feel bad that I spent so many years neglecting to treat patients better with thyroid hormone, but that is what I was taught in medical school. I know you're big on treating underlying conditions that can interfere with thyroid patients responding well to thyroid therapy. Not wanting to harm my patients any more than I did over the last twenty years, can you brief me on the scope of underlying conditions I should look for. If you post my email, please do it anonymously. I have been cautioned that a low profile is best for keeping my license to practice medicine.

Dear Doctor: Welcome to the rational, scientific side of clinical thyroidology. I don't know what caused you to jump ship from conventional (to me, commercial) medicine, but I'm pleased that you're sailing with us now.

Precautions, of course, are steps we take to avert harming the patients we treat with thyroid hormone. We take most of the steps in advance of the patient beginning thyroid hormone therapy. But we must take some steps, as I explain below, after the patient has begun treatment.

The precautions I take involve the following steps: (1) ensuring the cardiac safety of the patient, (2) learning his or her cortisol status, (3) determining whether he or she has blood sugar dysregulation, (4) making sure he or she both exercises regularly and (5) takes a wide array of nutritional supplements.

A company (Erfa Canada, Inc.) that markets a brand of desiccated thyroid gives an overview of prudent precautions with thyroid hormone therapy. The company's precautions are important. I recommend additional ones, but their precautions are worth quoting.

Patient' Cardiovascular Status: The company recommends: "Thyroid hormones should be used with great caution in a number of circumstances where the integrity of the cardiovascular system, particularly the coronary arteries, is suspect. These include patients with angina pectoris, hypertension, other cardiac conditions, or the elderly, in whom there is a greater likelihood of occult cardiac disease."

Some doctors unfortunately deny patients with delicate cardiovascular conditions any use of thyroid hormone. This is unfortunate because many of these patients can safely use and benefit from thyroid hormone; in fact, many cardiac patients must use thyroid hormone therapy to recover cardiac health.

Caution is the key to guiding these patients back to a healthy heart. The Erfa website describes a precautionary treatment approach: "In these patients, therapy should be initiated with low doses, i.e., 25 to 50 µg levothyroxine (T4) or its isocaloric equivalent (16 to 32 mg, or 0.25 to 0.5 grain of desiccated thyroid). When, in such patients, a euthyroid state can only be reached at the expense of an aggravation of the cardiovascular disease, thyroid hormone dosage should be *reduced*." (Italics mine.)

I agree with this cautious approach except for two things. First, the company mentioned the patient reaching a euthyroid state. This implies using a thyroid hormone dosage that keeps the TSH, free T4, and free T3 within their reference ranges. Bringing these hormones into their reference ranges, however, does *not* render most patients well. At its website, Erfa tells what does: "The principal pharmacologic effect of exogenous thyroid hormones is to increase the metabolic rate of body tissues." The safest and most efficient way to help patients get well is to free them from their symptoms by normalizing their metabolic rates. Hence, rather than a *euthyroid* state, we should instead strive for a *eumetabolic* state.

What I next disagree with is the company's advice that some cardiac patients start treatment with a T4 product. These products may not work at all for many cardiac patients, regardless of the dosages they use. If the patient is hypothyroid, I recommend a T4/T3 product with a T4 to T3 ratio of 4:1, or T3 alone. Some T4/T3 products with the proper ratio are Armour Thyroid, Nature-Thyroid, and Westhroid. I prefer the latter two products for two reasons. First, an occasional patient reports to me that when she takes Armour, she develops itching, which I assume is an allergic reaction. Switching to Nature-Throid or Westhroid relieves the itching. Second, the manufacturer of Nature-Throid and Westhroid, RLC Labs, goes to great lengths to ensure the quality, safety, and evidential basis of their therapeutic products. This is obvious in their description of how they formulate a variety of therapeutic products.

I always do an electrocardiogram (ECG) when I see patients personally. If I consult with a patient long distance, I also ask that he or she get an ECG from a local clinician and fax a copy of the tracing to me. I have two purposes for obtaining the ECG. First is to study the tracing for any evidence that aggressive thyroid hormone therapy is contraindicated. For example, my 12-lead electrocardiograph occasionally shows evidence of right heart damage and pulmonary hypertension in a patient who has used various weight-loss drugs. Second is to see whether the voltage of the patient's R wave is low. If it is, increasing voltage may serve as a useful physiologic barometer of metabolic improvement.

Erfa, in a statement I quoted above, suggests that thyroid hormone therapy may reveal "occult cardiac disease." This is true and important. Rarely, thyroid hormone therapy does unveil a cardiac problem that has been obscured over time by inadequate thyroid hormone regulation of the cardiovascular system. You mentioned that you have a copy of *The Metabolic Treatment of Fibromyalgia*. I recommend that you read the section on the heart (pages 875-888), especially the subsection titled "Worsening of the Manifestations of Coronary Heart Disease" on page 877. The entire chapter is about the safe use of thyroid hormone, but it's the heart that most practitioners are concerned about. I address those concerns and explain how to avoid adverse cardiac effects in patients using thyroid hormone. Except in the rarest cases, patients with fragile heart conditions can use thyroid hormone. But, again, caution is the key.

Erfa also mentions other precautions I strongly agree with: "Thyroid hormone therapy in patients with concomitant diabetes mellitus or insipidus or adrenal cortical insufficiency aggravates the intensity of their symptoms. Appropriate adjustments of the various therapeutic measures directed at these concomitant endocrine diseases are required."

Diabetes: I ask my patients to check their blood sugar regulation in two ways: (1) by taking several random measurements of their fasting blood sugar levels, and (2) by doing a 6-hour home glucose tolerance test (hGTT). These tests often show that a patient has glucose dysregulation. Some have fasting or reactive hypoglycemia, but most, in my clinical experience, have glucose intolerance.

In either case, too little glucose reaching a patient's cells can cause what I view as an energy crisis. This occurs when thyroid hormone therapy accelerates intracellular energy metabolism by increasing a wide range of enzymes, but the increased energy demand conflicts with too little energy substrate in the form of glucose. Clinicians and patients often misinterpret the resulting symptoms as thyrotoxicosis. In fact, glucose dysregulation is the primary source of the symptoms. And the symptoms block the patient from using a fully therapeutic dosage of thyroid hormone.

Cortisol Deficiency: I recommend salivary testing for ruling out a cortisol deficiency. Bear in mind, though, that if a patient's liver is underregulated by thyroid hormone, it may not clear cortisol from the body at a normal rate. The person's adrenal cortices are producing too little cortisol, but the slowed liver clearance leaves the body fluids with a reference range concentration of cortisol. But as thyroid hormone increases the patient's liver clearance of cortisol to a normal rate, the patient begins to develop cortisol deficiency symptoms. In this case, thyroid hormone therapy has unveiled an adrenocortical insufficiency. This phenomenon is similar to thyroid hormone therapy unveiling an occult cardiac disorder, which I mentioned above.

The precautions Erfa recommends are indeed important ones. However, in addition to those precautions, I also ask my patients to take two other precautions; that is, to exercise and take nutritional supplements.

Exercise: I ask my patients to regularly engage in stretching, resistance, and cardiovascular exercise to tolerance. Some patients have especially low cardiovascular and muscular fitness. Despite their low muscle fitness, their muscles tend to be chronically too tight. Most of these patients must begin exercise with baby steps, increasing the intensity of their workouts only after light exercise and thyroid hormone therapy increase their tolerance for the three types of exercise.

Stretching is helpful in temporarily reducing the excess muscle tightness caused by low muscle energy from too little thyroid hormone regulation. Muscle bulking exercise is important because lean body mass is the only factor that increases the resting metabolic rate more than does thyroid hormone. And aerobic exercise gradually increases the patient's level of cardiovascular fitness. This makes the heart more resistant to adverse effects from a dosage of thyroid hormone high enough to enable the patient to get well.

Nutritional Supplements: Next, I ask each patient to take a wide array of nutritional supplements, especially B complex vitamins. The importance of this can hardly be overemphasized.

If a patient hasn't been taking supplements, he or she may have borderline nutritional deficiencies. Many micronutrients function in cells as coenzymes. Thyroid hormone increases the production of many enzymes, causing a faster expenditure of their micronutrient coenzymes. When a patient doesn't take nutritional supplements, as thyroid hormone accelerates his or her metabolic rate, borderline nutritional inadequacies may become severe deficiencies. A deficiency of some B complex vitamins, calcium, or magnesium can cause nervous system and muscle hyperirritability. Clinicians and patients may mistakenly believe that too much thyroid hormone is at fault. In fact, the patient isn't even taking a fully therapeutic dosage of thyroid hormone.

A particularly harmful nutritional deficiency involves depletion of vitamin B1 from accelerated energy metabolism caused by thyroid hormone. The patient must regularly take in enough vitamin B1 to compensate for its increased intracellular expenditure. If he or she doesn't, a resulting B1 deficiency can cause beriberi-type cardiomyopathy—even though he or she is still taking too little thyroid hormone to recover from the hypothyroid symptoms.

This set of precautions and recommendations are the base from which I operate to ensure my patients' safety during thyroid hormone therapy. Keeping the precautions and recommendations in mind can make thyroid hormone therapy with a T4/T3 product or T3 alone truly effective. It can also provide your patients with the safety you're admirably concerned about. If you learn of other precautions that clinicians should be aware of, we'll be happy if you'll share them with the readers and staff of *Thyroid Science*. I wish you the most rewarding and prosperous sailing with natural medicine.

Cordially,
Dr. John C. Lowe
Editor-in-Chief
Thyroid Science

August 4, 2008

From the Editors:

We have just received notice that Thyroid UK, the thyroid patient advocacy organization in the United Kingdom, has officially received charity status. Thyroid UK has been working towards registered charity status for some time and after a lot of work, they have now achieved this.

Thyroid UK's objects are the relief of sickness of people suffering from thyroid disease and related illnesses, for the benefit of the public. To this end, those who work through Thyroid UK provide a number of humanitarian services. These include disseminating information and support to sufferers of thyroid disease; promoting public awareness of thyroid disorders; acting as a informational resource center; encouraging scientific research for the education, alleviation, care, treatment and cure of thyroid disease; and raising funds needed to achieve their objectives.

Lyn Mynott is Chief Executive of the organization. "Achieving registered charity status," she said, "will mean that we will be seen as a more professional organization and also that more funds will become available to us to achieve our objects."

Thyroid UK was recently been chosen by the Department of Health from over 120 applications to participate in the testing phase of a new scheme to ensure good quality information across the health and social care sector. Thyroid UK is the second largest thyroid charity in the UK and is an independent organization. It is run by patients for patients.

Dr. John C. Lowe, Editor-in-Chief of *Thyroid Science*, is proud to be a member of the Board of Medical Advisors of Thyroid UK. "Part of pride in being involved with Thyroid UK is the affiliation with Lyn Mynott. After being ill for 15 years and without knowing what was wrong, she had a thyroidectomy and treatment with thyroxine. This enabled her to regain her health. Lyn then began to campaign for better treatment, and she started a small support group that met in her living room. After appearing on BBC Watchdog Healthcheck in 1999, she was inundated with emails and phone calls. This spurred her on to set up Thyroid UK.

Thyroid UK's Contact Information: Tel: 01255 821733 Fax: 01255 820407
enquiries@thyroiduk.org www.thyroiduk.org

Subject: About *Thyroid Science*
From: Anonymous Reader
Date: Thu, June 19, 2008 10:21 am
To: Editor@thyroidscience.com

Dear Editor: I have been taking Eltroxin then later Synthroid since 1974. I discovered *Thyroid Science* just today. It is apparently a new publication? I would like information regarding the journal. Thank you

Dear Reader: *Thyroid Science* is an open-access electronic journal started a couple of
years ago by Dr. John C. Lowe's publisher, McDowell Publishing Company, LLC. It is committed to providing a publishing outlet for scientifically-oriented patients, clinicians, and researchers whose writings are usually censored by conventional endocrinology journals. The latter journals usually publish only papers that, as Dr. Lowe says, favor the financial interests of the drug companies that advertise in the journals. For all practical purposes, he says, those journals are ruled by advertising drug companies with the complicity of the endocrinology specialty. In contrast to those journals, *Thyroid Science* is dedicated to publishing papers without censoring their content to facilitate commercial interests. You are welcome to read anything published in *Thyroid Science*, and, if you wish, to contribute to the journal. I hope this answers your question.

Sincerely,
Tracy Majors
Assistant Editor
Thyroid Science (www.ThyroidScience.com)

Subject: Fine-needle aspiration and thyroid hormone resistance
Date: February 23, 2008
To: Editor@ThyroidScience.com
From: peter.warmingham@whsmithnet.co.uk

Dear Dr. Lowe: Are you aware of the paper by E Tjørve, KMC Tjørve, JO Olsen, R Senum, H Oftebro titled "On commmonness and rarity of thyroid hormone resistance: A discussion based on mechanisms of reduced sensitivity in peripheral tissues" (*Medical Hypotheses*, (2007) 69, 913-921)? In it the authors call for a test for peripheral resistance. Since the standard thyroid function blood tests don't serve this purpose. which of course the standard thyroid function blood tests don't. Maybe the fine-needle aspiration (FNA) technique used by Dr Bo Wikland and his colleagues would fit the bill?

Peter Warmingham, Thyroid UK Committee

Dear Peter: I have read the E Tjørve paper. I was pleased that Dr. Tjørve and his coauthors mentioned measuring the basal metabolic rate as a method for testing for resistance. I have used the test in my clinical practice for several years and published two studies so far using the method:

Report at *Medical Science Monitor:*
http://www.medscimonit.com/abstracted.php?level=4&id_issue=40182

(When you reach the page at *Medical Science Monitor*, scroll down to the second paper under "Clinical Research".)

Report at *Thyroid Science*: http://www.thyroidscience.com/studies/lowe.2006/lowe.2nd.rmr.fms.htm

Along with Tjorve et al, I believe that the basal or resting metabolic rate measurement is most useful clinically for identifying resistance patients, at least those with peripheral resistance. (Having peripheral resistance, of course, means that a patient's pituitary gland is normally or almost normally responsive to thyroid hormone, but most tissues peripheral to the pituitary are partially resistant.) Dr. Wikland's FNA identifies patients who have autoimmune thyroiditis despite reference range antithyroid antibody levels. Most of the patients are hypothyroid, which is the reason he and his colleagues term the disorder "subchemical hypothyroidism."

Some of these patients may also have peripheral resistance. But if they improve or recover with doses of thyroid hormone that are lower than supraphysiologic amounts, that would indicate that they are only hypothyroid and not resistant.

Most thyroid hormone resistance patients have to use supraphysiologic dosages of T3 to get well. Even T4/T3 products such as Armour usually don't work for them, not unless they use huge dosages, such as 12 grains or more. I have a book published in 1962 written by an endocrinologist—an endocrinologist from the time when many of them practiced clinical medicine rather than the extremist technocratic medicine of most endocrinologists today. In the book, the endocrinologist wrote that some of his "hypothyroid" patients didn't recover until they took as much as 60 grains of desiccated thyroid per day. I assume those patients really had peripheral resistance, as that amount would contain roughly 540 mcg of T3. That's truly a supraphysiologic daily dosage!

As I have, Dr. Wikland has found that most hypothyroid patients must suppress their TSH levels before they recover. I don't know the dosages his patients typically use, but if some of them use dosages that are well into the supraphysiologic range, the patients are probably partially resistant to thyroid hormone.

I use the following criteria to diagnose peripheral resistance: the patient has before treatment (1) hypothyroid-like symptoms before treatment, (2) reference range TSH and thyroid hormone levels, and (3) an abnormally low resting metabolic rate; and after treatment, he or she (4) recovers from his or her symptoms with a supraphysiologic dosage of plain T3 (5) with no evidence of thyrotoxicosis.

There are laboratory methods for testing for resistance. For example, we can use fibroblasts from a patient's skin. If a supraphysiologic amount of T3 is needed to inhibit the fibroblasts' synthesis and secretion of connective tissue constituents such as fibronectin, then the patient's cells (at least his or her fibroblasts) are resistant to thyroid hormone. I don't use this particular test for two reasons: first, it isn't available commercially; and second, even if it was, it requires a painful punch biopsy of the skin that I would prefer not to subject patients to.

To sum up, Dr. Wikland's FNA can certainly identify patients who are hypothyroid due to autoimmune thyroiditis. However, the procedure would not identify or rule out peripheral resistance to thyroid hormone.

Sincerely,
Dr. John C. Lowe
Editor-in-Chief
Thyroid Science

Subject: Re: *Thyroid Science*: Jan. 18, 2008, New Publications
Date: Fri, January 18, 2008 4:53 pm
To: Editor@ThyroidScience.com

Dear Dr. Lowe: Dr. Bo Wikland's paper (regarding treating euthyroid Hashimoto's patients with thyroxine) is unbelievably timely. I am seeing my doctor for the first time in over a month. I will be getting the results from my last full thyroid panel and hope to see a lowered antibody count.

I recently dosed up to 120mg of Armour and remained on the dose for three weeks prior to testing. At this point I need to bring my doctor up to date on what I've been trying to accomplish. I'm now up to 150mg of Armour and with the addition of Cortef to my program believe I may be beginning to get the improvement that I hoped for.

As my doctor views me as a "euthyroid Hashimoto's patient," it will be helpful to come armed with research as I try to get him onboard with my current strategy. My doctor and I have a good working relationship, and we go back many years. He's a long standing alternative doc and a good listener—so I am cautiously optimistic that all will go well. Thank you again for all that you, Tammy, and your staff do. Regards . . .

Dear Chris: I hope you're doctor responded well to Dr. Wikland's paper. One of our purposes at *ThyroidScience*.com is to provide patients like you with publications by experts in the thyroid field whose publications are often truncated and placed in inconspicuous places in endocrinology journals, or rejected for publication altogether to avoid offending the journals' advertisers

—usually ones that profit from T4-replacement therapy. I appreciate you writing. Your email lets us know that we're on the right track in publishing *ThyroidScience*.com.

Dr. John C. Lowe
Editor-in-Chief

Patient Asking Weather Thyroiditis Can Be Detected by Needle Aspiration in a Treated Patient? *Response to editorial on Dr. Bo Wikland*'s Research on Autoimmune Thyroiditis

December 7, 2007

Dear Dr. Wikland: I was very interested to read Dr. Lowe's editorial in Thyroid Science about "subchemical hypothyroidism," which you discovered and named. I am one of Dr Gordon Skinner's patients, and likely to get hung out to dry if the General Medical Council does its worst. I hope you can answer this for me, if you don't mind.

I was wondering whether the needle biopsy would still show anything useful in a clinically hypothyroid, but biochemically euthyroid, patient who has received treatment. I take 3.5 grains of Armour Thyroid.

Untreated, I had a TSH of 4.0 (reference range was 0.4-4.0) and a basal temp of 35 C-36.2 C (95 F-97.16 F). I was chronically fatigue for 28 years with other signs and symptoms (except I had normal reflexes for some reason). I had 'normal' levels of thyroid antibodies.

I cannot get treatment under our UK National Health System, as I can from Dr Skinner, because my TSH is now undetectable and my original need for thyroid replacement denied. So if this method would still show anything now (without my having to come off the Armour to satisfy anyone's curiosity now as to my untreated status), I would be very grateful to know. Dr Skinner is a bit busy just now, poor man.

Thank you and best wishes,
UK patient

Dear Belinda: Thank for your inquiry. I understand that you have achieved wellness on Armour Thyroid, but fear that you might be denied continued treatment in the UK because your TSH level is undetectable.

Having a desirable TSH level when on supplementary treatment with thyroid hormone is a hot potato. Mainstream opinion advocates "restoring TSH levels to normal," irrespective of patients' response to the treatment needed to achieve this. This is a *theoretical* point of view, which, when confronted with the patient's unsatisfactory response, very often proves to be wrong.

Our rationale for thyroid hormone replacement in autoimmune thyroid disease when the patient has symptoms of hypothyroidism is not to correct the hormone deficiency—the levels of circulating hormone, free T4 and free T3 are, usually appear normal. Rather, our intention with hormone supplementation is to mitigate autoimmune activity. Our hypothesis is that the TSH in this context is detrimental in promoting autoimmune activity. Therefore many (but not all) patients require a low level of TSH.

It is very unfortunate that patients requiring "suppressive" doses of thyroid hormone are denied adequate treatment. Patients are the best judges of their own health.

In the UK, there is one highly respected specialist, Dr. Anthony Toft, who advocates a flexible approach in managing treatment with thyroid hormone.[1] Fortunately, in Sweden where I practice, some clinical pathologists comment approvingly on a "suppressed" TSH that it is compatible with adequate supplementation.

I sincerely hope that you will be allowed the dose of thyroid hormone you require.

Reference

1. Toft, A.: Thyroid, 15:124-126. 2005.

Best wishes,
Bo Wikland, MD
Hötorget Medical Center
Sveavägen 13
SE-111 57 Stockholm, Sweden

Letters in Response to Dr. Lowe's Critique: Thyroid Hormone Replacement Therapies: Ineffective and Harmful for Many Hypothyroid Patients

On June 19, 2004, Dr. John Dommisse sent an email to Dr. Lowe in response to his critique of the replacement studies. Dr. Dommisse is a physician who practices nutritional, metabolic, and psychiatric medicine, and who hosts a popular telemedicine website. He is a member of the Endocrine Society, which publishes the *Journal of Clinical Endocrinology and Metabolism* (*JCEM*). *JCEM* published two of the replacement studies in 2003, and an editorial in which the authors reiterated the invalid conclusion of the endocrinologists who conducted the studies.

Dr. Dommisse's email included a copy of a letter he'd written to the Editor of *JCEM*. He wrote the letter in response to the reports of the replacement studies. *JCEM* declined to publish his letter, so he gave Dr. Lowe permission to publish it here as support for Dr. Lowe's critique.

In his email to Dr. Lowe, Dr. Dommisse wrote, "*JCEM* would not even publish a (longish, admittedly) LETTER that I wrote to the editor in response to that spate of bogus articles!"[1]

Dr. Lowe replied:

> I am not surprised that *JCEM* didn't publish your letter. I'm not surprised despite your letter's precise relevancy to the articles about the replacement studies, despite the excellent points you raised about treatment and avoiding adverse effects, and despite your clear prose. We became convinced long ago that, regarding the diagnosis and treatment of hypothyroidism, most major medical journals are not published in the pursuit of truth. If they were, they would provide for debate of dissenting views—as is traditional in real sciences. Instead, in our view, the purpose of the journals, in regard to the diagnosis and treatment of hypothyroidism, is to perpetuate medical acceptance of financially profitable beliefs and to censor dissenting views that might threaten financial markets nourished by those beliefs. What bothers me most is that, in my opinion, to serve those two purposes, those who decide what will and won't be published in those journals must carry on with cavalier disregard for the pernicious impact of those beliefs on humanity.[2]

Dr. Dommisse's full letter to the Editor of the *Journal of Clinical Endocrinology and Metabolism*

References

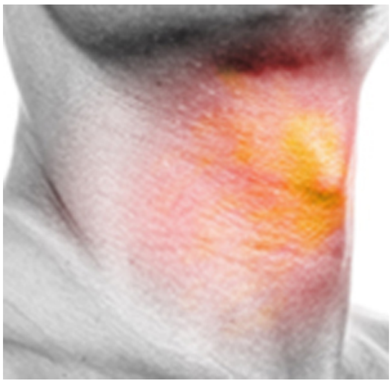
1. Dommisse, J.: Personal written communication with Dr. John C. Lowe. June 19, 2004.
2. Lowe, J.C.: Personal written communication with Dr. John Dommisse. June 19, 2004.

Subj: Brief Comment on Critique of Thyroid Hormone Replacement Studies
Date: 6/8/2004 4:47 PM Mountain Daylight Time
From: piek@waitrose.com
To: drlowe@drlowe.com
Sent from the Internet

Dear Editor: The original Bunevicius research found benefits for T3/T4 over T4 and was followed up by a further analysis (*Int. J. Neuropsycopharmacology*, 2000, 3:167-174) which demonstrated that these benefits applied only to those on

TSH-suppressive doses of thyroid hormones, particularly for thyroid cancer. Each of the four replacement studies tested patients on lower doses.

However, "Combined Thyroxine/Liothyronine [T4/T3] Treatment Does Not Improve Well-Being, Quality of Life, or Cognitive Function Compared to Thyroxine Alone: A Randomized Controlled Trial in Patients with Primary Hypothyroidism" (Walsh et al. *JCEM* 88(10):4543-4550) is a classic. ". . . subjects attended after an overnight fast and before taking T4 or study medication (i.e. 24 h after the previous dose)." Their data shows that the T3/T4 group had lower T3 levels than the T4 group and in the Discussion section they acknowledge the 24-hour half life of T3! Duh!!! Jim Harwood.
piek@waitrose.com



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Thyroid Science 3(1):1, 2008
Invited Editorial

Redefining Hypothyroidism: A New Paradigm

Bo Wikland, MD*

(Full Text Free in pdf format)

*Hötorget Medical Centre, Sveavägen 13, SE-111 57 Stockholm, Sweden,
Contact: bo.wikland@comhem.se

KEYWORDS: fine needle aspiration cytology, hypothyroidism, thyroid autoimmunity, thyroid autoantibodies

Introduction by Dr. John C. Lowe

Editor-in-Chief

We recently invited Dr. Bo Wikland of Stockholm, Sweden to write an editorial for *Thyroid Science*. We did so because of the importance of the research he and his colleagues have conducted and reported. That research involves what they term "subchemical hypothyroidism." After reading their reports in *The Lancet*, I noted this condition and its importance in a *Thyroid Science* editorial.

Here, however, Dr. Wikland himself explains to us the importance of this condition and how to diagnose it. His recognition of this clinical phenomenon and the solution he provides for patients suffering from it is nothing short of momentous. He calls for a paradigm shift in the diagnosis of hypothyroidism. In my view, such a shift is imperative: It is crucial to incalculable numbers of hypothyroid patients recovering their health, and it will be of vital interest to clinicians who are truly concerned about the well-being of these patients.

As Dr. Wikland explains, the shift he calls for entails including tissue evidence of thyroiditis in patients' diagnostic workups. This evidence can supplement biochemical test results that have indicated that patients are hypothyroid. Or, more importantly, the tissue evidence can show that the patient is hypothyroid when biochemical testing often fails to do so. Dr. Wikland uses and recommends tissue morphological evidence from "fine-needle aspiration cytology." (An informative website that explains find-needle aspiration cytology is available at no cost.) This diagnostic procedure has the potential to rescue patients whose clinicians would otherwise deny them the thyroid hormone treatment upon which their health and well-being depend. We are grateful to Dr. Wikland for composing his invited editorial for *Thyroid Science*.

Wikland, B.: Redefining Hypothyroidism—A Paradigm Shift. *Thyroid Science,* 3(1):1, 2008.

(Full Text Free in pdf format)

Thyroid Science 3(1):1, 2008 www.ThyroidScience.com *Invited Editorial*

Redefining Hypothyroidism—A Paradigm Shift

Bo Wikland, MD*

*Hötorget Medical Centre, Sveavägen 13, SE-111 57 Stockholm, Sweden, *Contact:* bo.wikland@comhem.se

Keywords: fine needle aspiration cytology • hypothyroidism • thyroid autoimmunity • thyroid autoantibodies

In the clinical investigation of patients with suspected thyroid disease, TSH is an established first-line test. A spontaneous low value raises the possibility of hyperthyroidism. A high TSH is considered to signify hypothyroidism. So far, things look straightforward.

In industrialised societies, most cases of hypothyroidism are the result of an autoimmune attack on the gland. So far, there is also general consensus.

Since the introduction of the TSH analysis, this test has become the most trusted single measure of the condition of the thyroid. The importance bestowed on the TSH necessitates a clearly defined reference range. Over the years, the lower range has undergone relatively small adjustments. What is regarded as a "high" value has, however, been subject to repeated downward shifts. Also, there are considerable inter-laboratory differences as to the upper limit of "normal." It is very unfortunate that today, there is no clear and universally accepted upper limit of "normal" for this crucially important test.

As autoimmunity is the leading cause of thyroid disease, it is important to document thyroid autoimmune activity. *Indirectly*, thyroid autoantibodies such as antibodies to thyroid peroxidase and thyroglobulin, and TSH receptor antibodies serve as evidence of thyroid autoimmunity.

A *direct* approach to demonstrate thyroid autoimmunity is to examine the gland by means of fine-needle aspiration cytology (FNA). For many years, this has been a routine procedure in our centre in Stockholm, Sweden. The diagnostic and therapeutic potential of FNA as a complement to conventional first-line tests is remarkable.[1][2] In summary, we found that no less than 40% of unselected patients with chronic fatigue (90% women) had definite evidence of lymphocytic invasion of the thyroid—the gold standard criterion of thyroid autoimmunity.

What about TSH in patients with FNA-documented evidence of thyroid autoimmunity? We found that TSH values were scattered, ranging from less than 1 mU/L to over 30; the median TSH value was 3.8.[1] (These were baseline values, and none of the patients were on thyroid medication.) In patients with cytologically-demonstrated thyroid autoimmunity, the clinical response to thyroid medication was equally favourable, regardless of the presenting TSH value.

Applying this experience to our everyday clinical practice, in patients with suspected thyroid imbalance, we must not rely on a "normal" TSH. Investigation should focus on thyroid autoimmunity, including analysis of thyroid autoantibodies, and, most desirably, FNA. This statement is not of mere academic interest; if the patient is a victim of overlooked thyroid autoimmunity/hypothyroidism, she (or he) will be condemned to continue a poor quality of life.

How, then, should we define hypothyroidism? It is obvious from the morphological findings that symptomatic autoimmune thyroid disease is far more common than revealed by biochemical assessment alone. In addition to conventional biochemical criteria (probably having a high diagnostic specificity), including morphological evidence of thyroid autoimmunity would substantially widen the scope to encompass more patients in need of thyroid medication. In my—and, above all, in the patients'—opinion, this is a welcome paradigm shift representing true progress.

References

1. Wikland, B., Löwhagen, T., and Sandberg, P.O.: Fine-needle aspiration cytology of the thyroid in chronic fatigue. *Lancet*, 357(9260):956-957, 2001.
2. Wikland, B., Sandberg, P.O., and Wallinder, H.: Subchemical hypothyroidism. *Lancet*, 361(9365):1305, 2003.

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Dr. Barry Peatfield

In Defense of Dr. Barry Peatfield

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An Introduction to the Case of Dr. Barry Peatfield

Dr. John C. Lowe

May 8, 2001

Dr. Barry Peatfield is a doctor who practices in Surrey, England, close to South London. He has long given patients a high-quality alternative to conventional medical care. He is immensely popular in the United Kingdom. His popularity comes from his having helped thousands of patients who had previously remained ill under conventional medical care.

To help patients recover their health, Dr. Peatfield has courageously subjected himself to threats of reprisal from conventional medicine, most notably from endocrinologists. But threats aren't all that conventional medicine has subjected him to. He has had to defend himself in the past before the General Medical Council at tremendous personal cost. Despite intimidation by some endocrinologists, and difficulties with the General Medical Council, he has bravely continued to use methods that safely and effectively relieve his patients' suffering. Now, he again faces possible suspension of his license. Many people, especially those who have recovered their health under his care, want to know why.

General Medical Council Considers Suspending Dr. Peatfield's License

A function of the General Medical Council is to make sure doctors practice in line with current medical guidelines. The conventional guidelines for diagnosing and treating hypothyroidism are dictated by beliefs of the conventional thyroid specialty (a "sub-specialty"of the endocrinology specialty). The two main beliefs this specialty has imposed on doctors are: (1) the TSH is the only test needed to diagnose and treat hypothyroid patients, and (2) T4 (thyroxine) is the only thyroid hormone preparation any hypothyroid patients need to take.

When a doctor violates these beliefs in his or her practice, a regulatory agency such as the General Medical Council in the United Kingdom may impose punishment. (In the United States, the agencies that enforce conventional guidelines are the state boards of medical examiners.) Few doctors, however, are called to account for the heresy of violating the guidelines for the diagnosis and treatment of hypothyroidism. Only high profile doctors are usually subjected to this. Dr. Peatfield is one such doctor. In fact, he is the most prominent alternative doctor in England. Little wonder, then, that he is the focus of attention of the General Medical Council. His high visibility makes the outcome of his case crucial. If his license is suspended, a paralyzing apprehension will instantly spread among less-prominent alternative doctors.

Most mainstream doctors embrace and comply with the beliefs of the conventional thyroid specialty. They do so partly from fear of punishment if regulatory agencies learn that they've violated the guidelines. But they also comply because they assume the beliefs are established scientific facts. The conventional thyroid specialty has encouraged this assumption. But as I documented in *The Metabolic Treatment of Fibromyalgia*,[1] the beliefs are *not* scientifically factual.

What is factual is that the conventional beliefs about the diagnosis and treatment of hypothyroidism are false propositions based on extraordinarily bad science. (See my letter to the General Medical Council.) In my opinion, the false propositions are also based partly on the corrupting influence of financial incentives. These incentives come from companies that profit from regulatory agencies forcing doctors' to follow the guidelines. (See section of my letter to the General Medical Council addressing financial incentives in the section titled "Use of Desiccated Thyroid".)

Why Doctors Comply with Conventional Guidelines

Over the years, scores of doctors have told me they complied with the guidelines from fear of regulatory agencies. When I've contended that the beliefs the guidelines are based on aren't scientific facts, many doctors have been astonished, skeptical, and vehemently disagreed. From these experiences, I've been impressed with the conventional endocrinology specialty's success at intimidating and misguiding other doctors.

I have been even more impressed, however, with a psychosocial phenomenon—the successful use by many conventional endocrinologists of the power of personality to induce compliance with the guidelines. I have known a few endocrinologists who were, in their interactions with other doctors, congenial and showed the hesitancy and tentativeness about beliefs that characterize scholars. In my experience, however, the conventional endocrinology specialty harbors more arrogance, dogmatism, sense of indisputable certainty, and claim to supreme authority than any other medical specialty. My impression is that this personality profile—which is uncharacteristic of scholars and professional scientists—has done more than even the punitive powers of regulatory agencies to induce compliance by other doctors. This profile is so common among endocrinologists, and so often offensive to patients, that many patients contemptuously call the specialists "endo-criminologists."

This personality profile, while powerfully persuasive, is distinctly *unscientific* conduct. The conventional thyroid specialty is also unscientific in its conduct in other ways. But unscientific conduct in general and the personality profile go hand in hand. I will describe the profile, but first, let me explain the more general unscientific conduct of many members of this problematic specialty.

Unscientific Conduct of the Conventional Thyroid Specialty. To provide a point of reference, let me briefly describe proper scientific conduct by medical researchers. Proper conduct involves researchers using sound reasoning to reach conclusions based on the results of studies. It involves reaching conclusions free from the influence of financial interests of those who fund the studies. It involves understanding that beliefs based on study conclusions are *always tentative*. It involves evaluating evidence by logical principles rather than the preconceived notions of authorities. It involves listening open mindedly to those whose interpretations of the study results differ from their own—regardless of the discipline or specialty of those with different interpretations. And proper scientific conduct involves openly—and open mindedly—debating those who argue that one's conclusions are not correct.[2][3][4][5][6]

In stark contrast to this scientific demeanor, consider the conduct that, according to my experience and study, typifies the conventional endocrinology specialty. (I hastily add that I'm acquainted with endocrinologists who are notable but rare exceptions to this generalization.)

First, researchers within the conventional thyroid specialty have reached conspicuously illogical conclusions from studies. Some of their illogical conclusions that have damaged the public health include, but aren't limited to, the following: (1) TSH-suppressive doses of thyroid hormone usually cause osteoporosis; (2) TSH-suppressive doses will increase threefold all patients' chances of atrial fibrillation; (3) a TSH within the reference range is proof that a patient can't possibly suffer from too little thyroid hormone regulation; (4) T4 therapy is invariably effective in treating hypothyroidism; (5) treatment with T4 is "superior" to treatment with desiccated thyroid; (6) T3 is a dangerous medication.

Second, some of their beliefs that have most damaged the public health have been based on grossly faulty research methodology. They have failed to use adequate controls in studies. They have misrepresented authoritative presumptions as factually established. And they've set up arbitrary definitions that have enabled them to sidestep criticisms of serious flaws in their conclusions and beliefs. This bad science discredits all beliefs of the specialty concerning the diagnosis and treatment of hypothyroidism.

Third, after having reached conclusions from studies, they have failed to properly consider them *tentative*—as *all* scientific beliefs *always* are. Instead, they have dogmatically promoted their conclusions as irrevocable scientific facts. They have also arrogantly disregarded reasonable and credible dissenting view of doctors and scientists outside their specialty. One way they've effectively disregarded these views is by using the peer review process to block their publication in mainstream journals. Intolerance of dissenting views is proper within the military and institutionalized religions, but it is utterly counter to acceptable scientific conduct.

Forth, conclusions the specialty has promoted as scientifically factual—especially regarding practice guidelines—are predictable based on the financial incentives provided by commercial interests that fund conventional thyroid research. For financial incentives to shape scientific beliefs is a gross deviation from the traditional bases of such beliefs, which were curiosity and the pursuit of truth.

Fifth, they have exerted political pressure so that regulatory agencies (such as the General Medical Council) punish doctors who disagree with their beliefs regarding hypothyroidism. This is *not* scientific conduct. Instead, it is the undemocratic imposition of their beliefs on doctors and patients through political force. (A profound British thinker, John Stuart Mill, would have called this conduct tyranny.[7]) If the conventional thyroid specialty's beliefs about hypothyroidism had scientific and practical merit, the specialty wouldn't have to impose the beliefs on doctors and patients through political force. The merit of the beliefs, revealed through benefits to patients, would induce acceptance. As Dr. Peatfield's case shows, however, the specialty *must* resort to political force. Its use of force is *ipso facto* evidence for the substantial demerits of their beliefs.

The Power of Personality and the Conventional Endocrinology Specialty. Actor Anthony Hopkins once explained how he prepared himself for the role of Dr. Hannibal Lecter in the movie *Silence of the Lambs*. He talked of the state of mind he had to adopt to effectively play the role. The state of mind was that typical of the charismatic dictator who melts the will of others, inducing them to obsequiously yield to his will and decrees. The dictator exerts this effect by a powerful personality feature—total, absolute, unwavering certainty that he is right, that he is the sole broker of truth.

Hopkins is correct about this personality feature. It promptly dissolves most people's resistance when in the presence of such a dictator. In his autobiography *Mein Kampf*, Adolf Hitler wrote explicitly about the use of this powerful personality feature. He used it as a tactic for vaporizing resistance to his political will. Historians have described many examples of Hitler exhibiting this power over others. Even many zealous opponents of Hitler, when finally in his presence, fell under his spell and, on the spot, changed to enthusiastic supporters. I trust that many who read this will recall displays of this personality feature in the offices of endocrinologists. Fortunately, many patients are strong enough that they've escaped the influence, left the endocrinologists' offices, and found alternative doctors, such as Dr. Peatfield, who have relieved their suffering by violating the guidelines. Most doctors, however, fall under the spell of this personal feature and accept the pronouncements of conventional endocrinologists as pure scientific truth.

This personality feature, unquestioning trust that the guidelines are factual, and threats of punishment by regulatory agencies have impelled mainstream doctors to comply with the practice guidelines. But Dr. Peatfield has admirably refused to comply.

Conclusion

I can think of only two legitimate questions anyone should ask about Dr. Peatfield's clinical practice. First, "Do his methods of practice get enough of his patients well?" The answer to this is a resounding yes. Thousands of patients and their loved ones in the United Kingdom will testify to this. Second, "Have his methods of practice harmed patients?" The answer is no.

If, then, Dr. Peatfield gets patients well, and he doesn't harm them, why is the General Medical Council subjecting him to possible license suspension? Because of his defiant refusal, on his patients' behalf, to comply with the conventional thyroid specialty's beliefs—false beliefs based on bad science, ego, medical politics, and subversion by commercial interests. It is my belief that the allegations against him are justifications contrived for punishing him for having defied an arrogant, dogmatic, tyrannical medical aristocracy. Essentially, he is being punished for having the strength of character to think for himself, the responsibility to give his patients safe and effective treatments, and the courage to face the political consequences.

Based on this view, I believe that suspension of Dr. Peatfield's license will betoken a disregard by the General Medical Council of the health and welfare of the public. As such, the license suspension should serve to rally patients, their loved ones, patient advocacy groups (such as Thyroid UK), doctors, and scientists. I believe these people should use the force of numbers to provoke legislation and litigation that will bring an end to the horrid legacy of the conventional thyroid specialty of the past thirty years. If a social movement amasses to cause change, the political persecution of Dr. Peatfield will have served a noble purpose. I will deeply regret, however, that such a fine human being and quality doctor will have been crucified in the process.

cc: Barry Durrant-Peatfield, M.B.

To help support Dr. Peatfield and the cause of alternative medicine, please read Mary Shomon's article on Dr. Peatfield's case. At the end of her article, she explains what you can do to help. Please move quickly, however. The outcome will be decided on Friday, May 11, 2001. <http://thyroid.about.com/library/weekly/aa042501a.htm>

Follow Up

For the outcome of Dr. Peatfield's case, see
Political Tyranny Prevails in England
<www.drlowe.com/news/recent.htm#Political Tyranny>

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Fibromyalgia Research Foundation
A Nonprofit Organization for Research and Education

April 17, 2001

Richard Clifford
Committee Section
Interim Orders Committee
General Medical Council
178 Great Portland Street
London W1W 5JE United Kingdom
Fax No: 0207 915 3696

Quote Ref No: FPD/2000/1704

Dear Mr. Clifford:

I am submitting the following letter as testimony on behalf of Dr. Barry Peatfield. I will be grateful if you will arrange for a copy to be provided to all relevant parties within the General Medical Council.

Preliminary Note: In this letter, I will refer repeatedly to the "mandates" of the conventional thyroid specialty. By mandates, I refer to four propositions that serve as guidelines to the diagnosis and treatment of hypothyroidism. The mandates are: (1) a deficiency of thyroid hormone is the only cause of symptoms and signs characteristic of hypothyroidism, (2) clinicians should not permit patients with "normal" thyroid test results to use thyroid hormone, (3) hypothyroid patients should use thyroid hormone only in "replacement dosages" (dosages that keep the TSH within its reference range), and (4) hypothyroid patients should only use thyroxine (T4). As I recently documented, each of these mandates is false.[1]

I use the term "mandates" to refer to the propositions for a specific reason: because the punitive powers of regulatory agencies, such as the General Medical Council, subjugate physicians to them. The powers of regulatory agencies of conventional medicine can be invoked to force physicians to use the diagnostic and treatment protocol dictated by the mandates. Those powers force physicians to comply with the mandates, even when the protocol the mandates decree clearly fails to meet the needs of the physicians' hypothyroid or thyroid hormone resistance patients. The powers can also be invoked to punish physicians who violate the mandates. The physicians may be punished even though violating the mandates was the only way to relieve the suffering of their patients.

Some physicians, such as Dr. Barry Peatfield, have steadfastly persisted in violating the mandates. Their doing so has been an act of courage, for the risk they have faced on their patients' behalf is suspension or revocation of the privilege to practice medicine.

Comments on Dr. Barry Peatfield's Medical Practice

Below, I comment on several issues involved in Dr. Peatfield's case with the General Medical Council. The issues include his (1) knowledge of the field of thyroidology, (2) choice of thyroid hormone preparations, (3) predominant use of patients' clinical status rather than laboratory test results, and (4) patient education program. I then make a concluding statement.

Dr. Peatfield's Knowledge of the Field of Thyroidology

I am especially qualified to comment on Dr. Peatfield's knowledge of the field of thyroidology. I am the author of a recently published textbook titled *The Metabolic Treatment of Fibromyalgia*.[1] In the book, I *comprehensively* covered both the field of thyroidology and that of fibromyalgia. In that I covered both fields, the book is actually two textbooks in one. The massive size of the book (1260 pages) was necessary for one purpose: to effectively argue that fibromyalgia is a clinical phenotype of inadequate thyroid hormone regulation of tissue function, I had to include in the book critiques of some 6,000 published papers and books.

I had the privilege of visiting Dr. Peatfield in England in October, 2000. I spent several days with him, intensely discussing thyroidology and fibromyalgia. During these discussions, we talked in great detail about his clinical practice. We spent considerable time discussing similarities and differences of his practice from those of other clinicians offering the public alternatives to the conventional medical treatment protocol for hypothyroid patients.

From these extensive discussions with Dr. Peatfield, I know that he has read my textbook cover to cover—all 1260 pages. Having written the book, I can, of course, easily discern from discussions with individuals who have and have not read it. Dr. Peatfield has done so, through and through. This is an enormous feat, considering the size of the book. That he has read the entire book is substantial evidence that he is intensely dedicated to acquiring cutting-edge knowledge of thyroidology. From my discussions with him, I know that his motivation for such burdensome study is to provide his hypothyroid patients with the highest possible quality of care. During the past thirty years, the conventional thyroid specialty has succeeded in abbreviating most physicians' knowledge of thyroidology to two false propositions. The first is that the TSH is the only test physicians need to identify and manage hypothyroid patients. The second is that the only thyroid hormone hypothyroid patients ever need to use is thyroxine. Dr. Peatfield is a stellar exception to this dwarfing of physicians' knowledge of thyroidology. I consider him one of the rare physicians today with a vast, rational, and current-state-of-the-field knowledge of thyroidology. In my estimation, his knowledge of thyroidology far exceeds that of all but a few endocrinologists I have communicated with during the past 15 years. Moreover, from my lengthy discussions with Dr. Peatfield and two of his assistants, I learned that in his management of hypothyroid patients, his decisions are based on thoughtful consideration of his vast knowledge of thyroidology. What more can one ask of a medical practitioner caring for hypothyroid patients.

Dr. Peatfield's Choice of Thyroid Hormone Preparations

Dr. Peatfield uses both desiccated thyroid and T3 in his clinical practice. Below, I discuss his use of each of these separately. First, however, I will comment on the inadequacies of thyroxine therapy that make the use of desiccated thyroid and T3 preferable in the treatment of hypothyroidism and partial cellular resistance to thyroid hormone.

Use of Thyroxine. Dr. Anthony Toft recently wrote that most hypothyroid patients being treated with thyroxine "have no complaints about their medication."[18] He made a similar statement in an October, 2000 letter to Mrs. Linda Thipthorp of Truro, Cornwall, England: "The overwhelming majority of patients receiving thyroxine therapy for an underactive thyroid gland in whom blood tests are normal feel perfectly well."[19]

Dr. Toft's enthusiastic endorsement of thyroxine treatment drew a rebuttal from Mary Shomon (the world's foremost advocate of patients dissatisfied with conventional medical treatment). "Toft's opinion," she wrote, "actually directly contradicts the findings of informal research conducted by the Thyroid Foundation of America that showed that the majority of post-Graves' disease hypothyroid patients still suffered a variety of symptoms when on levothyroxine."[20,p.153]

Indeed, contrary to Dr. Toft's opinion, available evidence shows *widespread* dissatisfaction with conventional thyroid hormone therapy dictated by the mandates. The mandate that physicians permit patients to use only thyroxine has generated tremendous dissatisfaction. My website, <www.drlowe.com>, is visited almost exclusively by patients dissatisfied with conventional thyroid hormone treatment. The site now has between 13,000 and 16,000 different visitors per month. Even stronger evidence for dissatisfaction is Mary Shomon's website, for hypothyroid patients displeased with their conventional treatment. Her site has an average of *half a million visitors each months!* Moreover, her book for hypothyroid patients dissatisfied with their conventional care, *Living Well with Hypothyroidism*,[20] was an instant bestseller. More than a year after its publication, its sales remain extremely high all across the English-speaking world.

Perhaps when Dr. Toft made the statements I quoted above, he had not been privy to such evidence. Regardless, the available evidence shows that his statement about patient satisfaction with thyroxine is wrong. Dr. Peatfield is well aware of this evidence. And his awareness contributes to his prudent and responsible decision not to treat his hypothyroid patients with thyroxine alone, but, instead, to treat them with desiccated thyroid or T3 alone.

I should mention that some researchers have concluded that treatment results with thyroxine are "superior" to those with desiccated thyroid.[31][32][33][34][35][36] In estimating which preparation was superior, some researchers mentioned the clinical status of patients in their studies. A thorough reading of the published papers, however, makes one thing clear: Most often, by "superior," the researchers have meant that thyroxine has provided free T3 levels more steadily within the reference range than has desiccated thyroid.[35] Hence, the researchers' aim in treating patients with thyroid hormone has been to keep the TSH and thyroid hormone levels within their reference-ranges. *The clinical and health status of patients has been of little or no concern.* The results of these studies, therefore, should *not* be interpreted to mean that thyroxine is superior in eliminating patients' hypothyroid symptoms and signs and returning them to a healthy status.

Use of Desiccated Thyroid. Dr. Peatfield prescribes desiccated thyroid or T3 for hypothyroid patients. The choice he makes depends on his mindful consideration of the individual patient's needs. His use of desiccated thyroid shows a freedom from the prejudicial and pejorative view of desiccated thyroid that predominates within the conventional thyroid specialty.

Consider, for example, Dr. Anthony Toft's recent statement, "Those who advocate the use of Armour thyroid do so on the basis of no evidence whatever . . ."[19] It is beyond my comprehension why anyone familiar with the thyroidology literature would make such an glaringly false statement. That desiccated thyroid, when used properly, is an effective and safe treatment for hypothyroidism is massively documented in the medical literature. In fact, through the first two thirds of the 20th century, most clinical studies within the field of thyroidology involved the use of desiccated thyroid. The published evidence that desiccated thyroid—in dosages twice to three times the equivalent amount of thyroxine prescribed nowadays by conventional physicians—is both safe and effective in the treatment of hypothyroidism is simply too massive to reference here.

In the 1970s, some pharmaceutical companies that market brands of thyroxine began providing enormous financial incentives to the conventional thyroid specialty. Until then, desiccate thyroid was far more widely prescribed than was thyroxine. Financial incentives from these companies continues and is gargantuan. Synthroid, for example, is a brand of thyroxine marketed by Knoll Pharmaceutical Company. Synthroid is one of the most frequently prescribed medications in the United States.

It is a fact of life that he who pays the Piper calls the tune. And when a corporation such as Knoll pharmaceutical Company donates a million dollars to the American Thyroid Society to fund thyroid research,[14] I am convinced that studies the Society funds with that money will be those whose outcomes are likely to be favorable to the financial interests of Knoll. This will ensure a continuing financial relationship between the Society, the funded researchers, and Knoll. Studies that would militate against the financial interests of the corporation are not likely to be funded. Similarly, when Knoll Pharmaceutical Company provides funding of the American Association of Clinical Endocrinologists (AACE) to develop practice guidelines,[15] those guidelines are likely to admonish physicians that the only form of thyroid hormone hypothyroid patients need is thyroxine.

I must also mention here that the use of TSH assays is enormous, providing immense revenues for companies that market them. Bulusu, a consultant chemical pathologist in England, wrote in 2000, "Most laboratories in the country are experiencing an exponential increase in workload for these tests. It is worrying that clinical diagnosis has been relegated to history, and that assessment is based almost entirely on biochemical tests." He referred to the "huge increases in work load and cost of doing these tests."[17] O'Reilly[16] wrote in 2000 that 890,000 TSH tests were performed in Scottish hospital laboratories alone. (TSH tests performed by non-National Health Service laboratories and those performed for screening for congenital hypothyroidism were not included in the calculation.) O'Reilly also wrote that the market for TSH assays in the United Kingdom (population of 59 million) is currently estimated at 9-to-10 million per year.

The large revenues from the marketing of thyroxine and TSH assays convince me that market forces powerfully dictate dynamics within conventional medicine so that the flow of money is stabilized. I raise this possibility to those within the General Medical Council because I believe it to be plausible, and if so, it seems to me a matter that must be investigated. Science and not financial incentives should be the basis of medical protocols that impact the lives of millions of human beings.

Some will consider it noblesse oblige of me to bring these matters up here. My rejoinder is that it would be ethically derelict of me not to. It is hard for me to imagine that rational considerations account for the intransigence of the conventional thyroid specialty toward those of us who consider its mandates pernicious to the health and well-being of patients. My opinion is that something other than rationality *must* account for the rigid adherence of the conventional thyroid specialty to mandates that so conspicuously fail to serve the interests of hypothyroid patients. In my view, it is well within the realm of possibility that, as with the industrial/military complex, the issue of human suffering and preventable death as a trade off for huge financial profits is an irrelevancy to corporate entities and individuals who profit from sales of thyroxine and TSH assays.

It therefore appears to me that financial incentives have been instrumental in shaping the conventional belief that thyroxine is "superior" to desiccated thyroid. Despite the advocacy of treatment with thyroxine, desiccated thyroid provided such satisfactory clinical results that physicians continued to prescribe it widely until the power of financial incentives changed the conventional medical preference to thyroxine. In addition, experimental studies comparing the effects of desiccated thyroid and thyroxine clearly demonstrate that desiccated thyroid is effective. Hence, I believe the conventional preference for treatment with thyroxine alone for the treatment of hypothyroidism has been financially rather than scientifically based.

After years of systematic and meticulous record-keeping and analyses of our data, we no longer use thyroxine alone in the treatment of hypothyroid patients. Our data showed that thyroxine alone provided such overwhelmingly inferior clinical results that we no longer can ethically restrict our patients to it. With most hypothyroid patients, we use either a synthetic T4/T3 combination or desiccated thyroid. Some hypothyroid patients do not benefit from these preparations but improve or recover only when we switch them to T3 alone.[3] Also, we have found that most biochemically euthyroid patients (those with "normal" thyroid function test results) with symptoms and signs characteristic of hypothyroidism improve or recover only with the use of T3 alone.

Use of T3. My research team has established that approximately 33% of fibromyalgia patients have laboratory-documented partial cellular resistance to thyroid hormone.[21][22] In addition, we have found in double-blind and case-control studies that the use of T3 therapy, within a context of a more comprehensive regimen of metabolic rehabilitation, is both safe and effective in enabling patients to markedly improve or fully recover from their hypothyroid-like symptoms and signs.[2][3][4][5][6][7][8][9]

After having studied my research team's published scientific papers and my textbook, *The Metabolic Treatment of Fibromyalgia*, Dr. Peatfield has astutely used

T3 therapy for the benefit of some patients. A sterling example of one of his patients who has recovered with the use of T3 alone is Mrs. Linda Thipthorp of Truro, Cornwall, England, whom I reference at other points in this letter. Dr. Peatfield uses T3 therapy appropriately, within the context of a broad-spectrum metabolic rehabilitation regimen. Having discussed at great length with him the diagnostic and treatment protocol within which he uses T3 therapy, I am convinced that he uses this thyroid preparation in his practice in a responsible, safe, and effective fashion.

Dr. Peatfield's Predominant Use of Patients' Clinical Status Rather Than Laboratory Test Values

Rather than laboratory tests, Dr. Peatfield depends chiefly on his patients' clinical status for making diagnostic and treatment decisions regarding hypothyroidism and thyroid hormone resistance. Using the patients' symptoms and their physical exam findings (sometimes called "clinical indices") clearly provides treatment outcomes superior to the use of laboratory testing. Interestingly, an excellent controlled study showing this was conducted in England by Fraser et al.[29] I summarized this study in *The Metabolic Treatment of Fibromyalgia*:[1,p.835]

> In 1986, Fraser and coworkers studied patients taking T4. Four clinicians experienced in the use of T4 evaluated the patients clinically and used the Wayne index. This index is a questionnaire used to indirectly evaluate metabolic status of patients through symptoms and signs. The clinicians classified patients as euthyroid, hypothyroid, or hyperthyroid. (It is obvious, by virtue of the form of assessment they used, that by these three terms, they meant, respectively, eumetabolic, hypometabolic, or hypermetabolic.) The clinicians' diagnoses were determined not to be biased by subjecting the Wayne index scores to the Kruskal-Wallis analysis of variance. *There was no significant difference in the median scores of the four clinicians.* By contrast, *tests of the total T4, total T3, free T4, free T3, and basal serum TSH were of no value in determining whether patients were taking enough, too little, or too much T4.* The researchers wrote, " These [laboratory] measurements are therefore of little, if any, value in monitoring patients receiving thyroxine replacement."[29] (Italics mine.)

Results of studies of the use of clinical indices by other groups, such as Johansen et al.,[30] are consistent with those of Fraser et al. Moreover, studies by Skinner et al.[12][13] and my research team[2][3][4][5][6][7][8][9] support the findings of Fisher et al and Johansen et al. As a result of such studies and his own research and clinical experiences, Derry has recommended that the use of the TSH test be abandoned.[26][27] Despite this experimental support published in the medical literature, regulatory agencies—probably at the behest of the conventional thyroid specialty—continue to threaten or actually impose punishments on physicians, such as Dr. Peatfield, who heed the message of these scientific studies and use clinical indices in lieu of laboratory test values in their practices. Despite the results of such studies, the conventional thyroid specialty has continued to promote the use of laboratory test values in lieu of clinical indices.

The available evidence indicates that conventional physicians' dismissal of patients' continuing symptoms and signs from the under-treatment or absence of treatment of hypothyroidism or thyroid hormone resistance has given rise to the "new diseases." These include fibromyalgia, chronic fatigue syndrome, and myalgic encephalomyelitis. An almost exclusive focus on the results of thyroid function test results, and neglect of the clinical and health status of hypothyroid patients, has become the standard of practice in conventional medicine.

Some conventional thyroid specialists deny this. For example, Toft and Beckett wrote, "Dr. O'Reilly . . . overstates his view that the clinical aspects of thyroid disease have been remarkably downgraded." They wrote further, "The correct diagnosis will usually be made on the basis of both clinical examination and the results of appropriate thyroid function tests."[10] Similarly, endocrinologist Kendall-Taylor, reacted to complaints that conventional thyroid specialists ignore patients' symptoms and signs. He protested, "The statement that 'the clinical features of hypothyroidism . . . have been relegated to the status of historical curiosities' is manifestly absurd: What the clinician aims to do is not simply categorize a patient into 'hyperthyroidism' or the subclinical variants, but rather to make a full diagnostic assessment, for which the thyroid function tests are one important facet."[28]

Seemingly verifying these defenses of the conventional medical protocol, endocrinologist Cassar recommended that patients not be permitted to use thyroid hormone unless the TSH is 10 mU/L or there is *"a compelling clinical indication."*[9] (Italics mine.) His use of the words "a compelling clinical indication" suggests that physicians should consider patients' symptoms and signs. The fact is, however, that such recommendations by conventional thyroid specialists are more academic and theoretical than real. I say this because conventional thyroid specialists have provided themselves with a rationale for disregarding symptoms and signs typical of hypothyroidism when these are inconsistent with the results of a patient's TSH level. In the face of such an inconsistency, the rationale is distinctly dismissive of patients' symptoms and signs. To wit: "Notwithstanding the physician's assurance that the T4 dose is optimal, and the demonstration that serum TSH has decreased into the normal range, these patients may ask for a larger dose or take a larger dose on their own initiative. In this setting, *the patient should be reassured that the T4 dose prescribed is appropriate, and other causes of the patient's complaints must be investigated.*"[11] (Italics mine.) (This statement is excerpted from Surks' chapter titled "Treatment of Hypothyroidism" in a major textbook on thyroidology, the 6th edition of *Werner's The Thyroid: A Fundamental and Clinical Text*, published in 1991.)

Surks' advice to reassure patients that their dose "is appropriate" *presumes* that the patient's T4 dose is adequate for the patient's individual needs. His advice that "other causes of the patient's complaints" be investigated shows a preconceived notion that replacement dosages of T4 are infallibly effective. In addition, his advice implies that if the patient is taking a replacement dose of T4 and is continuing to have symptoms typical of hypothyroidism, these *must* be caused by some other disorder. It is precisely this rationale of conventional thyroid specialists that has given rise to the supposed "new diseases" of the past 30 years: fibromyalgia, chronic fatigue syndrome, myalgic encephalomyelitis, and others—all largely the result of untreated or under-treated hypothyroidism or partial cellular resistance to thyroid hormone.[1][12][13][26][27]

As Dr. Gina Honeyman-Lowe and I have argued with substantial documentary evidence,[21][22] the disorder underlying most patients' fibromyalgia is inadequate thyroid hormone tissue regulation. Our data indicate that the fibromyalgia symptoms and signs of approximately 90% of patients are features of hypothyroidism and/or thyroid hormone resistance complicated by low physical fitness levels, nutritional deficiencies, the dysglycemic effects of poor diet, and adverse metabolic effects of various medications prescribed to control various symptoms of hypothyroidism and/or thyroid hormone resistance.

Many researchers have concluded that fibromyalgia and chronic fatigue syndrome are one and the same disorder.[23] Based on their comparative studies, it is highly probably that the etiology is the same as that of fibromyalgia—inadequate thyroid hormone tissue regulation. Other researchers who concur that fibromyalgia and chronic fatigue syndrome are features of untreated or under-treated inadequate thyroid hormone regulation include Dr. David Derry, former Scholar of the Medical Research Council of Canada,[26][27] and Dr. Gordon Skinner and Dr. Afshan Ahmad of Birmingham, Warwick, England.[12][13]

Epidemiological studies indicate that the incidence of fibromyalgia in different countries ranges from 2% to 13% of the populations.[24][25] If we are correct that the main underlying mechanism of fibromyalgia is inadequate thyroid hormone regulation of tissues, then the incidence of the fibromyalgic clinical phenotype alone in industrialized countries suggests that the mandates of the conventional thyroid specialty have caused a major public health crisis. When we include other clinical phenotypes (such has dyslipidemia and cardiovascular disease, depression, and chronic fatigue syndrome) in the calculation, the number of affected people totals scores of millions. This staggering figure suggests a shocking tragedy—that by imposing the mandates on physicians and their patients, the conventional thyroid specialty has caused the most colossal public health disaster in the history of medicine. It is my conclusion that this is precisely the legacy of the conventional thyroid specialty of the past thirty years.

The conventional thyroid specialty proclaims that it has established the "gold standard" for the diagnosis and treatment of hypothyroidism, expressed in their four mandates. Solving the problem of hypothyroidism by defining patients as "well" when their TSH and thyroid hormone levels are within the reference ranges, despite their continued suffering from hypothyroid-like symptoms and signs, is nothing more than a linguistic solution. The mandates, by dictating the choices of conventional physicians, have ruined the quality of life of millions of hypothyroid and thyroid hormone resistance patients. The mandates have also consigned uncountable numbers of people to premature death. It is noteworthy that Dr. Peatfield recognizes the pernicious effects of the mandates on hypothyroid patients, and that he has courageously chosen, on his patients' behalf, to practice in violation of the mandates.

I am convinced that the widespread use of clinical indices in the diagnosis and treatment of hypothyroid and thyroid hormone resistance patients would, with a few years, largely eliminate the putative "new diseases." But this rescue of millions of patients can occur *only* if physicians are permitted, with impunity, to conduct medical practices exemplified by that of Dr. Peatfield.

Dr. Peatfield's Patient Education Program

When my wife, Dr. Gina Honeyman-Lowe, and I visited Dr. Peatfield in England in October, 2000, he gave us copies of booklets he has authored on the various treatments he uses in his practice. He uses these booklets as patient education tools. The booklets contain educational information on thyroid hormone, hydrocortisone, and DHEA, and other agents. We noted that he took special pride in providing his patients with these materials so that they would be informed about the treatments they undergo with him. We talked with two of Dr. Peatfield's assistants who also described and took pride in his use of these educational materials for the benefit of his patients.

Dr. Honeyman-Lowe and I left England feeling that this aspect of Dr. Peatfield's clinical practice is exemplary, and that other physicians' patients would benefit from modeling his example. Having been particularly impressed with this aspect of Dr. Peatfield's practice, I am perplexed about the accusation that he has not adequately informed his patients about relevant aspects of hydrocortisone treatment. The accusation starkly contrasts with our observations.

One complaint against Dr. Peatfield apparently is that he has not informed patients of the need to *gradually* withdraw patients from physiologic doses of hydrocortisone. In general, I do not believe there is any indication to do so. The purpose of physiologic dosages of hydrocortisone is to compensate temporarily for decreased adrenal reserve, and a rebound deficiency upon abrupt withdrawal would be extraordinarily unlikely. This is especially so in that during the time Dr. Peatfield has patients taking physiologic dosages of hydrocortisone, the patients are also undergoing thyroid hormone therapy. If a patient, before beginning treatment with Dr. Peatfield, had decreased adrenocortical function due to inadequate thyroid hormone regulation, the thyroid hormone therapy will have increased adrenocortical function. As a result, when the patient stops taking the physiologic dosage of hydrocortisone, his or her adrenal cortices should be able to synthesize and secrete sufficient amounts of cortisol. Thus, in general, the results are distinctly different from that in patients taking pharmacologic dosages of hydrocortisone.

Dr. William McK. Jefferies has championed the safe uses of cortisol.[37] Dr. Peatfield's use of this therapeutic agent is vindicated by Jefferies research and other explorations of this subject.

Conclusion

For the past fifteen years, I have been intensely engaged in research and clinical practice directly related to thyroidology. Based on this experience, I am convince that the mandates of the conventional thyroid specialty for the diagnosis and treatment of hypothyroidism are responsible for a world-wide public health crisis. The available evidence indicates that within this crisis, incalculable millions of people subjected to medical practices based on the mandates remain ill, disabled, or die prematurely from heart attacks, strokes, or suicide.

Physicians such as Dr. Barry Peatfield are doing their small part to rectify the damage by violating the mandates in their clinical practices. To do so, they courageously risk punishment by regulatory agencies such as the General Medical Council. Rather than being punished, however, these physicians should be honored by medical societies for their courage and humanitarian efforts. In addition, regulatory agencies should take it upon themselves to recognize the human suffering and premature death caused by the mandates of the conventional thyroid specialty, and they should call that specialty to account for its horrifying legacy of the past thirty years.

I will be happy to elaborate, in writing or in person, any of the viewpoints I have expressed in this letter. The public health ramifications of the mandates of the conventional thyroid specialty are gravely serious. Because of this, I urge the General Medical Council to both exonerate Dr. Peatfield, and to address the pernicious impact of the mandates on the health and well-being of citizens of the United Kingdom.

Best regards,
Dr. John C. Lowe
Chiropractic Physician
Board Certified: American Academy of Pain Management
Director of Research: Fibromyalgia Research Foundation
<www.drlowe.com>

cc: Barry Durrant-Peatfield, M.B.

Follow Up

For the outcome of Dr. Peatfield's case, see
Political Tyranny Prevails in England
<www.drlowe.com/news/recent.htm#Political Tyranny>

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An Introduction to the Case of Dr. Barry Peatfield

Dr. John C. Lowe

May 8, 2001

Dr. Barry Peatfield is a doctor who practices in Surrey, England, close to South London. He has long given patients a high-quality alternative to conventional medical care. He is immensely popular in the United Kingdom. His popularity comes from his having helped thousands of patients who had previously remained ill under conventional medical care.

To help patients recover their health, Dr. Peatfield has courageously subjected himself to threats of reprisal from conventional medicine, most notably from endocrinologists. But threats aren't all that conventional medicine has subjected him to. He has had to defend himself in the past before the General Medical Council at tremendous personal cost. Despite intimidation by some endocrinologists, and difficulties with the General Medical Council, he has bravely continued to use methods that safely and effectively relieve his patients' suffering. Now, he again faces possible suspension of his license. Many people, especially those who have recovered their health under his care, want to know why.

General Medical Council Considers Suspending Dr. Peatfield's License

A function of the General Medical Council is to make sure doctors practice in line with current medical guidelines. The conventional guidelines for diagnosing and treating hypothyroidism are dictated by beliefs of the conventional thyroid specialty (a "sub-specialty"of the endocrinology specialty). The two main beliefs this specialty has imposed on doctors are: (1) the TSH is the only test needed to diagnose and treat hypothyroid patients, and (2) T4 (thyroxine) is the only thyroid hormone preparation any hypothyroid patients need to take.

When a doctor violates these beliefs in his or her practice, a regulatory agency such as the General Medical Council in the United Kingdom may impose punishment. (In the United States, the agencies that enforce conventional guidelines are the state boards of medical examiners.) Few doctors, however, are called to account for the heresy of violating the guidelines for the diagnosis and treatment of hypothyroidism. Only high profile doctors are usually subjected to this. Dr. Peatfield is one such doctor. In fact, he is the most prominent alternative doctor in England. Little wonder, then, that he is the focus of attention of the General Medical Council. His high visibility makes the outcome of his case crucial. If his license is suspended, a paralyzing apprehension will instantly spread among less-prominent alternative doctors.

Most mainstream doctors embrace and comply with the beliefs of the conventional thyroid specialty. They do so partly from fear of punishment if regulatory agencies learn that they've violated the guidelines. But they also comply because they assume the beliefs are established scientific facts. The conventional thyroid specialty has encouraged this assumption. But as I documented in *The Metabolic Treatment of Fibromyalgia*,[1] the beliefs are *not* scientifically factual.

What is factual is that the conventional beliefs about the diagnosis and treatment of hypothyroidism are false propositions based on extraordinarily bad science. (See my letter to the General Medical Council.) In my opinion, the false propositions are also based partly on the corrupting influence of financial incentives. These incentives come from companies that profit from regulatory agencies forcing doctors' to follow the guidelines. (See section of my letter to the General Medical Council addressing financial incentives in the section titled "Use of Desiccated Thyroid".)

Why Doctors Comply with Conventional Guidelines

Over the years, scores of doctors have told me they complied with the guidelines from fear of regulatory agencies. When I've contended that the beliefs the guidelines are based on aren't scientific facts, many doctors have been astonished, skeptical, and vehemently disagreed. From these experiences, I've been impressed with the conventional endocrinology specialty's success at intimidating and misguiding other doctors.

I have been even more impressed, however, with a psychosocial phenomenon—the successful use by many conventional endocrinologists of the power of personality to induce compliance with the guidelines. I have known a few endocrinologists who were, in their interactions with other doctors, congenial and showed the hesitancy and tentativeness about beliefs that characterize scholars. In my experience, however, the conventional endocrinology specialty harbors more arrogance, dogmatism, sense of indisputable certainty, and claim to supreme authority than any other medical specialty. My impression is that this personality profile—which is uncharacteristic of scholars and professional scientists—has done more than even the punitive powers of regulatory agencies to induce compliance by other doctors. This profile is so common among endocrinologists, and so often offensive to patients, that many patients contemptuously call the specialists "endo-criminologists."

This personality profile, while powerfully persuasive, is distinctly *unscientific* conduct. The conventional thyroid specialty is also unscientific in its conduct in other ways. But unscientific conduct in general and the personality profile go hand in hand. I will describe the profile, but first, let me explain the more general unscientific conduct of many members of this problematic specialty.

Unscientific Conduct of the Conventional Thyroid Specialty. To provide a point of reference, let me briefly describe proper scientific conduct by medical researchers. Proper conduct involves researchers using sound reasoning to reach conclusions based on the results of studies. It involves reaching conclusions free from the influence of financial interests of those who fund the studies. It involves understanding that beliefs based on study conclusions are *always tentative*. It involves evaluating evidence by logical principles rather than the preconceived notions of authorities. It involves listening open mindedly to those whose interpretations of the study results differ from their own—regardless of the discipline or specialty of those with different interpretations. And proper scientific conduct involves openly—and open mindedly—debating those who argue that one's conclusions are not correct.[2][3][4][5][6]

In stark contrast to this scientific demeanor, consider the conduct that, according to my experience and study, typifies the conventional endocrinology specialty. (I hastily add that I'm acquainted with endocrinologists who are notable but rare exceptions to this generalization.)

First, researchers within the conventional thyroid specialty have reached conspicuously illogical conclusions from studies. Some of their illogical conclusions that have damaged the public health include, but aren't limited to, the following: (1) TSH-suppressive doses of thyroid hormone usually cause osteoporosis; (2) TSH-suppressive doses will increase threefold all patients' chances of atrial fibrillation; (3) a TSH within the reference range is proof that a patient can't possibly suffer from too little thyroid hormone regulation; (4) T4 therapy is invariably effective in treating hypothyroidism; (5) treatment with T4 is "superior" to treatment with desiccated thyroid; (6) T3 is a dangerous medication.

Second, some of their beliefs that have most damaged the public health have been based on grossly faulty research methodology. They have failed to use adequate controls in studies. They have misrepresented authoritative presumptions as factually established. And they've set up arbitrary definitions that have enabled them to sidestep criticisms of serious flaws in their conclusions and beliefs. This bad science discredits all beliefs of the specialty concerning the diagnosis and treatment of hypothyroidism.

Third, after having reached conclusions from studies, they have failed to properly consider them *tentative*—as *all* scientific beliefs *always* are. Instead, they have dogmatically promoted their conclusions as irrevocable scientific facts. They have also arrogantly disregarded reasonable and credible dissenting view of doctors and scientists outside their specialty. One way they've effectively disregarded these views is by using the peer review process to block their publication in mainstream journals. Intolerance of dissenting views is proper within the military and institutionalized religions, but it is utterly counter to acceptable scientific conduct.

Forth, conclusions the specialty has promoted as scientifically factual —especially regarding practice guidelines—are predictable based on the financial incentives provided by commercial interests that fund conventional thyroid research. For financial incentives to shape scientific beliefs is a gross deviation from the traditional bases of such beliefs, which were curiosity and the pursuit of truth.

Fifth, they have exerted political pressure so that regulatory agencies (such as the General Medical Council) punish doctors who disagree with their beliefs regarding hypothyroidism. This is *not* scientific conduct. Instead, it is the undemocratic imposition of their beliefs on doctors and patients through political force. (A profound British thinker, John Stuart Mill, would have called this conduct tyranny.[7]) If the conventional thyroid specialty's beliefs about hypothyroidism had scientific and practical merit, the specialty wouldn't have to impose the beliefs on doctors and patients through political force. The merit of the beliefs, revealed through benefits to patients, would induce acceptance. As Dr. Peatfield's case shows, however, the specialty *must* resort to political force. Its use of force is *ipso facto* evidence for the substantial demerits of their beliefs.

The Power of Personality and the Conventional Endocrinology Specialty. Actor Anthony Hopkins once explained how he prepared himself for the role of Dr. Hannibal Lecter in the movie *Silence of the Lambs*. He talked of the state of mind he had to adopt to effectively play the role. The state of mind was that typical of the charismatic dictator who melts the will of others, inducing them to obsequiously yield to his will and decrees. The dictator exerts this effect by a powerful personality feature—total, absolute, unwavering certainty that he is right, that he is the sole broker of truth.

Hopkins is correct about this personality feature. It promptly dissolves most people's resistance when in the presence of such a dictator. In his autobiography *Mein Kampf*, Adolf Hitler wrote explicitly about the use of this powerful personality feature. He used it as a tactic for vaporizing resistance to his political will. Historians have described many examples of Hitler exhibiting this power over others. Even many zealous opponents of Hitler, when finally in his presence, fell under his spell and, on the spot, changed to enthusiastic supporters. I trust that many who read this will recall displays of this personality feature in the offices of endocrinologists. Fortunately, many patients are strong enough that they've escaped the influence, left the endocrinologists' offices, and found alternative doctors, such as Dr. Peatfield, who have relieved their suffering by violating the guidelines. Most doctors, however, fall under the spell of this personal feature and accept the pronouncements of conventional endocrinologists as pure scientific truth.

This personality feature, unquestioning trust that the guidelines are factual, and threats of punishment by regulatory agencies have impelled mainstream doctors to comply with the practice guidelines. But Dr. Peatfield has admirably refused to comply.

Conclusion

I can think of only two legitimate questions anyone should ask about Dr. Peatfield's clinical practice. First, "Do his methods of practice get enough of his patients well?" The answer to this is a resounding yes. Thousands of patients and their loved ones in the United Kingdom will testify to this. Second, "Have his methods of practice harmed patients?" The answer is no.

If, then, Dr. Peatfield gets patients well, and he doesn't harm them, why is the General Medical Council subjecting him to possible license suspension? Because of his defiant refusal, on his patients' behalf, to comply with the conventional thyroid specialty's beliefs—false beliefs based on bad science, ego, medical politics, and subversion by commercial interests. It is my belief that the allegations against him are justifications contrived for punishing him for having defied an arrogant, dogmatic, tyrannical medical aristocracy. Essentially, he is being punished for having the strength of character to think for himself, the responsibility to give his patients safe and effective treatments, and the courage to face the political consequences.

Based on this view, I believe that suspension of Dr. Peatfield's license will betoken a disregard by the General Medical Council of the health and welfare of the public. As such, the license suspension should serve to rally patients, their loved ones, patient advocacy groups (such as Thyroid UK), doctors, and scientists. I believe these people should use the force of numbers to provoke legislation and litigation that will bring an end to the horrid legacy of the conventional thyroid specialty of the past thirty years. If a social movement amasses to cause change, the political persecution of Dr. Peatfield will have served a noble purpose. I will deeply regret, however, that such a fine human being and quality doctor will have been crucified in the process.

cc: Barry Durrant-Peatfield, M.B.

To help support Dr. Peatfield and the cause of alternative medicine, please read Mary Shomon's article on Dr. Peatfield's case. At the end of her article, she explains what you can do to help. Please move quickly, however. The outcome will be decided on Friday, May 11, 2001. <http://thyroid.about.com/library/weekly/aa042501a.htm>

Follow Up

For the outcome of Dr. Peatfield's case, see
Political Tyranny Prevails in England
<www.drlowe.com/news/recent.htm#Political Tyranny>

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Fibromyalgia Research Foundation
A Nonprofit Organization for Research and Education

May 1, 2001

Richard Clifford
Committee Section
Interim Orders Committee
General Medical Council
178 Great Portland Street
London W1W 5JE United Kingdom
Fax No: 011-44-2079-153696

Quote Ref No: FPD/2000/1704

Dear Sirs and Madams of the General Medical Council:

I am the Education Director of the Fibromyalgia Research Foundation in the United States. I have also worked for years with Dr. John C. Lowe, helped in his research, and am Editor of his book, The Metabolic Treatment of Fibromyalgia. Dr. Lowe has studied thyroid function in countless patients, both in research and clinical settings. We have learned a great deal.

It is my job to educate patients about thyroid function and how it is involved in hypothyroidism, fibromyalgia, and chronic fatigue syndrome. I do this from a non-technical, non-clinical viewpoint since I am not a medical practitioner. I am a patient trying to help educate other patients about what we have learned through our extensive research. The goal of this work is better treatment for patients.

I have prefaced my remarks with statements about myself because I am one representative of the millions of people with undiagnosed thyroid disease. I write in support of Dr. Barry Durant-Peatfield and other clinical medicine doctors everywhere who are trying to alleviate the suffering of their patients.

My condition remained undiagnosed for so many years because the tools used were blood tests. It was only through the clinical expertise of Dr. Lowe and his colleagues that I am a healthy person today. The use of thyroid hormone should not be restricted to people with aberrant blood tests. People with normal blood tests but who have clinical signs and symptoms can safely use thyroid hormone since thyroid hormone is one of the easiest medications to monitor.

With many drugs, deleterious effects can only be seen over the long term. With thyroid hormone, however, clinical effects—both harmful and beneficial—are manifest over days or weeks. In the hands of a doctor like Dr. Peatfield, who is trained to look at his patient rather than the blood tests of that patient, clinical monitoring is so much more successful than any blood test in the treatment of that patient. There are no studies that show long term harmful effects from a thyroid hormone dosage perfectly suited to normalize the metabolism of the patient. I submit, as do no doubt most of the people who have written to you, that the only proper method to determine such a dosage is through the type of clinical treatment that Dr. Peatfield, Dr. Lowe, Dr. Honeyman-Lowe, and all the others like them perform.

In addition, well-documented thyroid conditions such as peripheral cellular resistance to thyroid hormone are undetectable through blood tests. The abnormal clinical status of a patient with normal blood tests is what points toward the diagnosis. Unless doctors learn to observe their patients' signs and symptoms (and stop allowing the blood tests to make the diagnosis), many of these conditions will continue to be missed and countless numbers of patients will continue to suffer.

Dr. Barry Durant-Peatfield, for his tireless work for the welfare of his patients, should be given an award for clinical medicine, not a dressing-down from the GMC. Should it not be the job of the GMC to make sure the top priority in all considerations is the welfare of patients? On behalf of all those patients who have not and will not receive the help they need without doctors like Dr. Peatfield, I ask you to do your job. Please, think of the patients, not the politics of the situation.

Sincerely,
Jackie Yellin
Education Director
Fibromyalgia Research Foundation, U.S.A.
www.drlowe.com

cc: Barry Durrant-Peatfield, M.B.

Follow Up

For the outcome of Dr. Peatfield's case, see
Political Tyranny Prevails in England

Questions and Answers

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Q&As

March 22, 2011
Question: Do you know why my levels of free T4 and free T3 would drop after I started taking Armour thyroid? I wasn't taking thyroid hormone before, and my doctor said this is an odd reaction. Is there something my doctor can fix so that my free T4 and T3 will rise, as it's supposed to by taking Armour?

Dr. Lowe: A person's free T4 and free T3 can decrease after beginning Armour for at least 2 reasons I know of.

Malabsorption. One is poor absorption of the hormones in the intestine. The malabsorption may result from what we currently call "lymphocytic colitis."

Lymphocytic colitis is a chronic inflammation of the lining of the intestinal wall. The condition appears to be more common among middle-aged to elderly women. The inflammation swells the lining just beneath the fingers (villi) that extend from the intestinal wall into the passage way of the intestines. The swelling from the inflammation compresses the capillaries that carry nutrients, drugs, and other substances from the colon passage way into the blood. The compression reduces the nutrient rich blood that reaches the general body circulation. For some clients I've consulted with, using a Medrol Dosepak (methyl-prednisolone) or a prednisone dosepak for the usual 5 days reduces or eliminates the inflammation and swelling. The people then recover normal absorption. I've never seen harm from the very short-term use of prednisolone or prednisone. Of course, to keep the inflammation from returning, it's crucial in my view that the person adopt a anti-inflammatory diet (a paleo-diet or a Meditarrainian diet), and take anti-inflammatory supplements. These include omega-3 fatty acids, Boswellia, and many others.

In some people, impaired absorption is usually caused by inflammation of the lining of the small intestine rather than the colon. The inflammation may be caused by an antigen-antibody reaction to gliadin (the peptide in gluten to which antibodies form), soy, casein in milk, or other antigens. Ordering lab tests to learn which food constituents you have antibodies against is obviously important. When you know what the food constituents are, you can avoid them or minimize your consumption of them.

Failed compensation for ingested Armour. T3 absorbs from the GI tract into the blood far more efficiently than T4. If enough T3 in the Armour (9 mcg per grain) absorbs into the blood, it can suppress TSH secretion. The reduced TSH will then lower the amount of T4 and T3 that the thyroid gland secretes.

Here's the critical point to understand: The thyroid gland might reduce its output of the two hormones far enough that the T3 absorbed into the blood from the intestine doesn't adequately compensate for the reduced thyroid gland output of T4 and T3. From too little T3, then, the person might then develop abnormally low metabolism and symptoms of hypothyroidism.

Conversion of T4 to reverse T3 rather than T3. There's a second potential mechanism for your low free T4 and free T3. In most people, T4 is preferentially converted to reverse-T3 rather than T3. In the average person, as much as 60% of T4 through the day and night is converted to reverse T3 rather than T3. Reverse T3, of course, is metabolically inert. The conversion to reverse T3 is catalyzed by the enzyme called "5-deiodinase." This is a separate enzyme from "5'-deiodinase." That little apostrophe mark after the "5" means we call this enzyme "5-prime deiodinase." This is the enzyme that converts less than 50% of T4 to T3.

Acutely high cortisol or chronically high mercury are well-documented to inhibit 5-prime deiodinase. When this enzyme is inhibited, rather than T4 converting to T3, even more converts to reverse T3.

This could result in free T4 and free T3 becoming lower in their reference ranges. The person might also become hypometabolic and develop hypothyroid symptoms. This would occur because the metabolically-inactive reverse T3 competitively binds to thyroid hormone receptors. This blocks the metabolically-active T3 from combining to them. I hope this helps.

Sept.29, 2010
Question: My pharmacist told me that the company that makes Armour Thyroid is filing bankruptcy. Does this mean Armour Thyroid may not be available again? Any advice?

Dr. Lowe: On May 13, 2010, Bloomberg business new and ABC news

Dietary or Over-the-Counter Desiccated Thyroid

Continued from bottom of left column . . .

February 10, 2004
Question: You read where you said that Forest Pharmaceuticals doesn't actively market Armour Thyroid or go after those who bad mouth the product. Do you know why?

Dr. Lowe: A representative at Forest Pharmaceuticals told me that what seems like indifference by the company is strictly a business decision. Forest could pay for studies to show that Armour is as stable and effective as any other thyroid hormone product. But the studies could cost as much as three millions dollars, and this wouldn't be cost effective for the company. The reason is that the projected increase in sales of Armour wouldn't make the investment in the studies financially worth while. Besides, Armour Thyroid sells quite well based on its effectiveness compared to competitive products.

February 8, 2004
Question: A doctor told me that Armour Thyroid is named Armour because the shape of the thyroid gland is like a shield. Do you know if this is true?

Dr. Lowe: I doubt it, mainly because the gland is shaped more like a butterfly than a shield. Nonetheless, I've occasionally heard what the doctor told you about the origin of the name Armour Thyroid.

Until today, I had no idea whether or not it was true. I checked my dictionary to see if it contained any helpful information. I found that a meat-packing industrialist, who lived from 1832 to 1901, was named Philip Danforth Armour. This raised a question as to whether Armour Thyroid bears his name.

To find out, I contacted a representative of Forest Pharmaceuticals, the company that markets Armour. He told me that the origin of the name isn't certain, but most likely, the first drug company to market the product named it after Armour Meat Company of St. Louis, Missouri. This was the company Philip Danforth Armour owned. The Forest representative said that slaughtering of animals at the meat-packing company made thyroid tissue available for medical use.

The representative wasn't sure when the product was first marketed, but he thinks it goes back at least to 1940. I've often heard, without verification, that Armour has been on the market for a hundred years or so. He commented that there's a problem in knowing the product's true lineage: Forest is the 4th or 5th company to own the right to market Armour, and former companies usually don't pass along to successive companies a detailed history of the product. He told me that Forest, which is based in St. Louis, acquired the right to market Armour from a French drug company, bringing it back to its geographic birthplace.

December 9, 2003
Question: I'm a 49 year old woman who has suffered from chronic fatigue and fibromyalgia since I was a child. After reading some of your material, my doctor is willing to try treatment for hypothyroidism. She is recommending using Thyrolar because she is unsure of the origins of desiccated thyroid. What is your opinion as far as natural vs. synthetic as a treatment option? Are both equally effective?

Dr. Lowe: Armour Thyroid is desiccated thyroid derived from pig thyroid gland tissue. Most of our hypothyroid patients use Armour, and they respond extremely well to high enough dosages.

Sales representatives from one particular drug company have deceptively misled doctors into believing that the animal source of Armour makes its thyroid hormone content unreliable. The product's potency, however, is as reliable as that of any synthetic product. For patients who don't want to ingest animal products, Thyrolar is an excellent synthetic alternative to Armour. Armour and Thyrolar have the same ratio of T4 to T3. They are equally reliable and effective when patients use high enough doses.

Armour and Thyrolar both contain 38 mcg of T4 and 9 mcg of T3. This is 4 parts T4 to 1 part T3 (the exact ratio is 4.22 to 1).

Some endocrinologists now advocate the use of products containing both T4 and T3, but they recommend a higher T4 to T3 ratio. They prefer a ratio 10 parts T4 to 1 part T3. The lower T3 content of such products renders them far less effective than Armour and Thyrolar. In our clinical experience, the treatment outcome is inferior for patients who use products with the lower T3 announced that Forest Laboratories may file Chapter 13 bankruptcy and lay off 1200 employees. The reason for the company considering bankruptcy is from trouble from what the news agencies called "*legal* tax evasion." The news agencies reported that Forest "dodges taxes" by moving its profits offshore with a currently legal method called "transfer pricing." In the words of US Senator Carl Leven, transfer pricing "is the corporate equivalent to secret offshore accounts of individual tax dodgers." Senator Leven's office stated that the offshore tax havens Forest cost Americans about $100 billion per year.

That Forest is considering a Chapter 13 bankruptcy rather than a Chapter 7 suggests a brighter future for Armour Thyroid and Thyrolar, the two thyroid products of the company. With a Chapter 7 bankruptcy, a company may go completely belly up. If so, it's debts are partly discharged or perhaps wiped out altogether. A Chapter 13 bankruptcy is essentially a reorganizing process. It allows a company to reorganize its finances under the supervision of a federal bankruptcy court. The court monitors a payment plan between the borrower and the creditor. You can read more about this story at the ABC News website.

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April 5, 2009
Question: My doctor prescribed Armour Thyroid hoping it would work better than the Synthroid I had taken for years. Within a couple of weeks, my energy was up and I generally felt better. But I had to stop taking it because my skin itched all over. The itching started several days after I started taking the Armour. My doctor switched me back to Synthroid. The itching stopped, but within a couple of weeks, I was as miserable as I've always been on Synthroid. She switched me back to Armour, thinking that my itching had been coincidental, but the itching started again, so I'm now on Synthroid again and miserable again. Any advice?

Dr. Lowe: Your experience in switching back and forth from Synthroid to Armour is consistent to my observations of many patients. They are miserable on Synthroid (or other brands of T4), but although they improve remarkably on Armour, they itch or have other allergic symptoms. I've confirmed that the itching and other symptoms on Armour are allergy-based by having the patients go through a simple test. I have them take 25 mg to 50 mg of Benadryl while still using Armour. If the itching or other symptoms stop within thirty-minutes to an hour, then most likely, the patient is having an allergic reaction, probably to some of the binders or fillers, such as cornstarch. Further confirmation that the itching is an allergic reaction comes from the patient beginning to itch again after the antihistamine effects of Benadryl to wear off.

When patients have reported to me that they've had allergic reactions to Armour, I've recommended that they ask their prescribing clinicians to switch them to Nature-Throid. This product, produced and marketed by RLC Labs, is different from other prescription desiccated thyroid products. The difference is that it contains binding ingredients that are hypoallergenic, such as microcrystalline cellulose. Patients who have switched to Nature-Throid have maintained the benefits they got from switching from Synthroid to Armour, but in addition, they've freed themselves from their allergic reactions to Armour.

August 22, 2005
Question: When my family doctor found that I'm hypothyroid, she referred me to an endocrinologist. When I saw him, he prescribed Synthroid. I asked him to prescribe Armour, but he snapped at me, saying he's never prescribed anything but Synthroid, and since it works perfectly well, he's not going to prescribe anything else. He was very intense about not prescribing Armour. I guess he was angry that I'd asked him twice for Armour instead of Synthroid because he looked like he was going to burst at the seams. He said, "Go ahead and get somebody else to prescribe Armour. The T3 in it will make your T3 blood level peak in a couple of hours, and then you'll have heart palpitations, nervousness, and insomnia." Then he snapped at me: "When that happens, don't come whining to me. Go back to whoever was stupid enough to prescribe the Armour for you." I was shocked at how rude he was. That was my first and last trip to his office. His rudeness aside, if the peak T3 level is really such a problem, why do so many people prefer Armour to Synthroid?

Dr. Lowe: The answer is that the endocrinologist is mistaken; the peak T3 level is *not* a problem. The only time Armour causes adverse effects is when a patient takes too much for her as an individual—just as when she takes too much of any other thyroid hormone product, including Synthroid.

We've observed many hundreds of patients taking products that contain T3. Despite our careful inquiries of many of these patients, we've never heard complaints of adverse effects that could credibly be ascribed to peak T3 blood level.

My impression is that most endocrinologists have had little-to-no clinical experience with T3-containing products. Perhaps because of that, they haven't learned that the adverse effects from peak T3 levels that they so often warn against seldom if ever occur. Their false belief that adverse effects do occur, however, serves well the financial interests of corporations that market T4 products, such as Synthroid. Some endocrinologists may not be cognizant of it, but when they parrot this false belief, they're taking part in their profession's *quid pro quo* for the enormous financial and content.

The inferior treatment outcome is supported by two recent studies conducted by endocrinologists.[1][2] The studies showed that patients who added only a small amount of T3 to their T4 continued to suffer from symptoms, just as did patients who used T4 alone. The ratios of T4 to T3 the patients used varied, but most used a higher T4 to T3 ration than in Armour and Thyrolar. Of course, the endocrinologists restricted the patients' dosages according to their TSH and thyroid hormone levels, and this almost guaranteed that the patients took too little thyroid hormone and continued to suffer from hypothyroid symptoms.

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Tammy@drlowe.com

Our Educational Consulting Service

We provide educational consulting to both patients and clinicians. Phone us at 603-391-6061, or preferably, write to us at Tammy@drlowe.com. Our fax number is 303-496-6200. ***—Tammy Lowe***

November 21, 2003
Question: I was recently diagnosed with Hashimoto's/hypothyroidism. But I've been sick with my hypothyroid symptoms for years. My endocrinologist put me on 1 grain of Armour Thyroid and scheduled me to return in about ten weeks for lab tests.

After four weeks, I called him and complained. I actually felt worse than before I started the Armour. He told me to come in and have blood work done, so I went in the next day. Two days later, his nurse called me with the results. My TSH 1.16 (it was 1.24 before I started the Armour), and my free T3 and free T4 were slightly above the middle mark. He told me my results were "textbook perfect," but I talked him into raising my dose to 90 mg.

I've been on the 90 mg for two weeks and my symptoms haven't gotten any better. I do aerobic exercise and weight training every day except Sunday. I also stick to a low glycemic type diet. My lifestyle is good, and I don't think it's what's holding me back from getting better. I'm getting frustrated and it's hard to keep up the positive attitude. I'm slowly getting depressed about not getting better, but there's not much more I can do. I already work my butt off. Should I press the endocrinologist to increase my dose further?

Dr. Lowe: It's good that you have an endocrinologist willing to prescribe Armour for you. Most endocrinologists are T4 bigots; yours isn't, and that's refreshing and fortunate for you.

Hopefully the endocrinologist won't keep your Armour dose too low. He most likely will, however, if he adjusts your dose according to your TSH and thyroid hormone levels while ignoring your clinical response to a particular dose. To get well, some patients must use Armour doses that are high enough to produce TSH and thyroid hormone levels that upset endocrinologists. But the lab values are meaningless in themselves, as long as a patient isn't over stimulated and has gotten well from her hypothyroid symptoms. What's truly harmful is for a doctor to keep a hypothyroid patient's dose too low strictly for the sake of predetermined lab values.

You said that your endocrinologist scheduled you for a reevaluation ten weeks after you started using Armour. Two to four weeks is usually enough time to evaluate the benefits, if any, from a particular dose of Armour. I see no reason to wait ten weeks for a reevaluation.

On the other hand, I hope you don't allow yourself to sink into depression because you haven't gotten any better after two weeks on 90 mg of Armour. Impatience is understandable since you've suffered from hypothyroid symptoms for years. But a little more patience is necessary to find your optimal dose. Armour contains both T4 and T3. The benefits you'll eventually get from the product will be a combined effect of the T4 and T3. If you increase your dose of Armour, and the increased dose contains enough T3 to benefit you, you're likely to see the benefit within a few days to a week. But you may not benefit from the T4 for one to four weeks. To see how you benefit from both the T3 and T4 in the Armour, you must wait out the lag time of up to four weeks. Hopefully you'll wait patiently; otherwise, you're likely compound the frustration you must already feel.

If a new dose of Armour contains too little T4 and T3 to benefit you, you'll have to go through another evaluation period. And nonfinancial incentives that T4-marketing corporations lavish on their specialty. (I document this in my soon-to-be published book *Tyranny of the TSH*.)

What should a patient, such as you, do when an endocrinologist espouses the false belief and then refuses to prescribe a T4/T3 product such as Armour. She should insist that the endocrinologist back up the belief with scientific evidence. What she'll get instead, however, is an authoritative pronouncement that the adverse effects do occur, which boils down to nothing more than thoughtless mouthing of a marketing script.

Incidentally, I regret that the endocrinologist was ill-mannered toward you. You're now a member of the huge population of hypothyroid patients who've reported gratuitous rudeness by members of that specialty.

Perhaps many endocrinologists are rude to patients such as you because they feel vulnerable. After all, they really have no scientific defense for prescribing only T4 products, which are ineffective for and harmful to many patients. In general, their choice of Synthroid is not based on science; instead, it's based on the flagrant conflict of interest between high-profile opinion-makers in their specialty and, in the US, Abbott Laboratories, which markets Synthroid.

Most endocrinologists restrict their hypothyroid patients to T4-replacement. But no hypothyroid patient today has to settle for this inferior and dangerous treatment. Thousands of doctors not on the take from Abbott now offer safer and more effective thyroid hormone therapies. For your own health and well-being, I encourage you to find one of these other doctors.

(I have elsewhere covered the false belief that peak T3 levels from the use of T3-containing products cause adverse effects. Please see sections in my critique of Dr. Richard Guttler's false and harmful beliefs about hypothyroidism, and my critique of recent T4 vs T4/T3 studies.)

November 27, 2004
Question: Six months ago, I was losing a lot of hair. I started studying hair loss and found out it might be caused by a thyroid problem. I went to see my doctor, and as it turned out, I was right. My TSH level was 20.8. My doctor said I'm hypothyroid and prescribed 75 mcg of Synthroid. Since I've been using the Synthroid, I've felt worse and worse, and my hair is still falling out. My doctor says that since my TSH is now 1.8, the Synthroid is working fine. After studying more, I found out that many hypothyroid people don't do well with Synthroid but get better with Armour. My doctor has talked it down, saying that in lab test studies, Synthroid worked better. He said that if I take Armour, the T3 in my blood will peak, and that may cause me to have a heart attack. I don't want to risk that. At 27 years old, I'm not ready to die. What are my other options? Is there some other treatment I can get, or am I doomed to stay on Synthroid, feel horrible, and lose all my hair?

Dr. Lowe: Your best options are to reeducate your doctor or find one who's more knowledgeable about thyroid hormone therapy. I suspect that your doctor has been mislead by two groundless beliefs promulgated by the endocrinology specialty—beliefs with disastrous consequences for hypothyroid patients such as you. The beliefs are about potential harm from using thyroid hormone products, such as Armour, that contain T3 as well as T4.

The endocrinology specialty first promotes the belief that *only* a steady blood level of T3 is normal and healthy; it follows through with a second, corollary belief: that is, if the T3 blood level peaks briefly, as after taking Armour, the patient is in peril. He'll probably have troubling heart palpitations, but worse, he may drop dead from a heart attack. The way around these potential problems, says the specialty, is to use T4 alone, as in Synthroid.

It is true that for some atients, a brief peak T3 level is indeed dangerous. But these patients aren't likely to walk into doctors' offices and ask for Armour or T3. The reason is, they're lying on their death beds in nursing homes, and a sip of coffee or tea might make their fragile hearts shutter and threaten to stop beating.

True, the hearts of these decrepit patients may not tolerate peak T3 levels well. This doesn't mean, however, that the same is true of the hearts of *all* patients. But concluding that it *is* true of all is an absurdly invalid deduction the endocrinology specialty has made.

For most patients, the brief peak T3 level from T4/T3 or T3 products is entirely inconsequential. I have observed— *scrutinized* is more accurate—many hundreds of patients who were using Armour or plain T3. Not a single one complained of troublesome palpitations during the peak T3 level. And not one reported a symptom during that peak T3 time that intimated an impending heart attack. In fact, no patient reported a symptom that suggested even a mild heart dysfunction.

The belief that the peak T3 level is troubling or dangerous for most hypothyroid patients has no scientific grounds. But as a scare tactic, it is an excellent marketing strategy. The belief has undoubtedly frightened hundreds of thousands of doctors, such as yours, into prescribing Synthroid in lieu of Armour. And as a result, it's led to the sustained suffering of millions of patients, such as you.

The solution to this problem—as with so many other health problems today—is to reeducate your doctor. Or, if his mind is closed, the solution is to find another one who already knows how to treat you safely and effectively. Best of luck at it.

More on the Endocrinology Specialty's *Presumption* that
T3 Adversely Affects the Heart

Continued at top of right column . . .

you'll have to do this again and again until you find what I call your "therapeutic window"—a small dosage range that optimally benefits you without over stimulating you. That optimal dosage range is highly individual, but historically, the typical patient's therapeutic window has been somewhere between 120 to 240 mg (2 to 4 grains). There's no way to accurately predict what your therapeutic window is. Until you find it, you may not improve much from the Armour. But once you do, you're likely to feel that the wait was well worth it.

November 12, 2003
Question: I've read in some of your articles about Armour Thyroid being used for people who don't respond well to Synthroid, and that they do quite well on Armour. I asked my doctor to change me from Synthroid to Armour. She absolutely refused. She said Armour is dangerous and is about to be taken off the market. Is all this true?

Dr. Lowe: No—Armour is *not* dangerous when patients use it properly, and it's *not* about to be taken off the market.

When most hypothyroid patients first consult me, they're using Synthroid. Some of them have been using it for only six months; others have used it for as long as thirty years.

These hypothyroid patients consult us mainly for one of two reasons. First, some have suffered from the same hypothyroid symptoms at the same intensity for so long—despite their use of Synthroid—that they're weary of it. Other patients' hypothyroid symptoms have gradually worsened to an intolerable degree, despite their continued use of Synthroid.

After we've evaluated these hypothyroid patients, a prescribing doctor on our treatment and research team switches them to Armour Thyroid—the product with which all our hypothyroid patients begin metabolic rehab. We then guide the patients through rehab. Within one-to-three months, virtually every one of the patients fully recovers her health—that is, she becomes completely free of hypothyroid symptoms.

Despite your doctor's opinion, none of these patients are harmed in any way by using Armour. Our treatment protocol includes painstaking monitoring for possible adverse effects from thyroid hormone. Our safety monitoring over many years has given us ample objective evidence that our hypothyroid patients' use of Armour is entirely safe. And our record of Armour's safety is consistent with that in the published research literature; that literature contains no evidence whatever of a danger in the use of Armour.

The long history of patients' safe use of Armour makes clear the professionally responsible course of action for your doctor: First, she should educate herself about Armour's safety record. Second, she should seriously contemplate the harm she's likely to do to patients by restricting them to chronic hypometabolism through her exclusive use of Synthroid.

Some of our hypothyroid patients who recover with Armour subsequently become extremely angry. Some were ill with hypothyroid symptoms for *decades*, while their endocrinologists or other conventional doctors forced them to use the most expensive thyroid hormone product, Synthroid. Then they're well after only a couple months use of the least expensive thyroid product, Armour. To me, their anger at and contempt for their former doctors is quite understandable.

Some doctors, such as yours, have recently spread gossip about Armour Thyroid being removed from the market. I've just now spoken by telephone with an official at Forest Pharmaceuticals, the company that produces and markets Armour. She was firm that the company has no intention of ceasing to produce and market Armour. Its sales are stable. They're stable despite unscrupulous marketing methods—such as spreading malicious gossip about Armour—by some of Forest's competitors in the drug industry, and by some endocrinologists who are complicitous with those competitors.

Hence, you can disregard your doctor's opinion as false. Patients have safely used Armour for a hundred years, and it will continue to be prescribed by doctors who are committed to getting their hypothyroid patients well. These doctors will be able to continue prescribing Armour because Forest Pharmaceuticals has every intention of keeping this excellent product on the market.

I wish you the best in finding a doctor who'll switch you to Armour. After the switch, I trust that you'll—like so many of our patients—recover from any hypothyroid symptoms the Synthroid has left you with.

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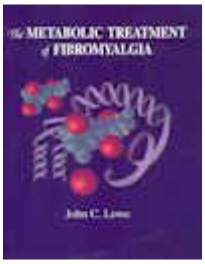

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[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

April 24, 2002

Question: I read that you and your wife, Dr. Gina Honeyman-Lowe, don’t work with patients taking narcotic medications for fibromyalgia. Since many fibromyalgia patients must use narcotics for pain relief, why do you feel this way?

Dr. Lowe: First, let me clarify our position regarding patients' use of narcotic medications. We make no value judgments about patients using narcotics, and we personally have no objections to patients choosing to do so. When patients use narcotics on an occasional, as-needed basis, this doesn't interfere with them improving or recovering when they go through metabolic rehab. We've learned, however, that most patients using maintenance doses of narcotics (taking them each day at intervals through the day) fail to benefit from metabolic rehab.

We have roughly an 85% success rate with fibromyalgia patients; that is, only about 15% of patients who fully cooperate with our protocol and complete treatment fail to markedly improve or fully recover. Prominent among this 15% who fail to recover are patients using maintenance doses of narcotic medications. We've tried to learn why these patients fail to improve and found two main problems.

The first problem is that narcotics appear to sensitize some brain centers to thyroid hormone. The evidence for this is sketchy, but the little evidence we've found provides a plausible explanation for an observation of ours: Some fibromyalgia patients taking maintenance doses of narcotics develop symptoms of over-stimulation at doses of thyroid hormone too low to enable them to recover. The apparent over-stimulation makes it impossible to raise their doses of thyroid hormone to therapeutic levels. When this becomes obvious, the only practical choices for the patients are to stop their narcotics or discontinue metabolic rehab.

With *some* patients who must make one of these choices, the second problem then arises. These patients don't want to stop the narcotics. Without hesitation, they choose to forgo the chance to improve or recover with metabolic rehab rather than give up the narcotics.

When we and our cotreating doctors have pressed these patients to stop the narcotics, they come to exhibit a complex of "drug-seeking behaviors." One behavior is hostility toward us for suggesting that they've become addicted to the narcotics. Objective measures may indicate that the pain of some of them has improved, but they'll insist that they’re still in pain and must continue using the narcotics. On the other hand, some patients indicate that they’re in 100% pain even with narcotic use. Despite this, they refuse to consider that since the narcotics haven't improved their pain at all that they should cease using them—at least temporarily—to give a promising alternative approach a chance to work. We’re convinced that some of these patients want to maintain a diagnosis of fibromyalgia as a ploy to continue their narcotic use.

As a pain management specialist, I was slow to face the reality of narcotic addiction of some fibromyalgia patients. The reason is that several years ago, I agreed that doctors were too restricted in their privilege of prescribing narcotics for patients in incorrigible pain, and I favored loosening of the restrictions. But as a fibromyalgia specialist determined to get each of our patients well, I have no choice but to face the fact that narcotic addiction becomes an obstacle to some patients' recovery.

I want to emphasize an important point: We know that narcotic use is a boon to many patients who live with chronic pain from which there is no available escape, and we have no objection to such patients using narcotics. Most patients' fibromyalgic pain, however, is escapable, although narcotic addiction often becomes a roadblock to the escape.

Unfortunately, discussing this subject openly carries a distinct risk. Many patients using narcotics—including some doctors with a diagnosis of fibromyalgia who liberally prescribe narcotics for their patients—promptly join campaigns of hostility toward doctors who express concern about narcotic addiction. We have no choice, though, but to be honest with patients using narcotics who inquire about treatment with us. For us not to discuss the subject forthrightly would be unethical.

The patient using narcotics and who wants to undergo treatment with us has two options. First, she can, before starting treatment with us, enlist the cooperation of the doctor who prescribes her narcotics in helping her stop the medication. Or she can commit to stopping the narcotic (again with the cooperation of the prescribing doctor) shortly after beginning metabolic rehab. If a patient chooses to continue taking maintenance doses of a narcotic, the chance of treatment failure with us is high. Again, we make no value judgment about a patient's choice either way, but professional ethics compel us to be honest about the issues involved. I hope this clarifies our position on fibromyalgia patients' use of narcotic medications.

January 24, 2002

Question: Are you aware of the fibromyalgia drug called milnacipran that Cypress Bioscience is working on? If you are, what do you think of it?

Dr. Lowe: Milnacipran is a drug that acts on two neurotransmitters, serotonin and norepinephrine, involved in pain modulation. The intent of this drug as a fibromyalgia treatment is to decrease patients' pain.

I'm certainly in favor of fibromyalgia patients, if they must, prudently using some drugs to control their symptoms—at least until they undergo effective metabolic rehab to correct their symptoms' underlying cause. I don't question that Cypress Bioscience is motivated by a desire to relieve the suffering of fibromyalgia patients. And I don't doubt that the corporation believes that providing milnacipran is an expeditious way to accomplish that desire.

At the same time, projects such as Cypress Bioscience's development of milnacipran cause me grave concern. To develop milnacipran as a fibromyalgia treatment, and to get FDA approval for the drug, involves a huge financial investment by the corporation. For me, that investment represents a troubling implication. The corporation (if it's run competently) must recoup its investment and produce profits. For this to happen, the corporation must count on the drug working well as a stop-gap method for reducing fibromyalgia patients' pain. The corporation must also either be (1) unaware that an effective treatment that corrects the underlying causes already exists, or (2) count on an indefinite delay in patients becoming aware of that cause-correcting treatment.

My personal belief is that the project by Cypress Bioscience is exactly what we don't need in the field of fibromyalgia: another corporation developing a patentable drug that does nothing more than reduce fibromyalgia patients' pain. Instead, we need to focus on the underlying causes of the pain. Only by focusing on underlying causes can we truly free fibromyalgia patients from their pain and other symptoms. The approach of Cypress Bioscience (if milnacipran is effective) will only reduce patients' pain while the causes continue apace.

Merely providing drugs that diminish symptoms rather than eliminating causes has long been a strategy of medically-related corporations for providing themselves long-term financial profits. Typically in modern medical science, a corporation comes up with a drug that modestly controls the major symptom of a disorder. Then the corporation begins to successfully market the drug. At that point, market forces come to militate against researchers eliminating the cause of the disorder. The corporation usually heavily funds a group of researchers in the field, and this group conducts steadily more studies related to that particular drug. These researchers' study results are readily published in major medical journals where the corporation pays lavishly to advertise the drug. In addition, the corporation sponsors (through financial-donations) well-publicized conferences where these researchers present their study results. The minds of practicing doctors are potently influenced by the highly visible published reports and conference presentations of these corporate-sponsored researchers. The practicing doctors presume that the drug represents the cutting-edge of science in the field.

This collaborative venture of corporations, researchers, major medical journals, and conferences effectively controls the minds of practicing mainstream doctors and their patients. Through this control, the venture easily undermines the work of other researchers studying the underlying causes of the disorder—causes that may be totally unrelated to the drug. Subverted in this way, the other researchers' work at best dimly shows through a veil of obscurity; their work remains poorly funded and largely ignored. Hence, the causes of the disorder persist and patients remain ill, yet those involved in the venture reap continuing financial rewards.

These observations bring me personally to conclusions that Cypress Bioscience probably won't like. First, to develop milnacipran as a fibromyalgia treatment is an expenditure of time, energy, and money that could be *far* better spent in clarifying the underlying causes of fibromyalgia. Second, this effort by Cypress Bioscience (and similar ones by other corporations) forebodes an ominous future for fibromyalgia patients under mainstream medical care.

Q&As

Diabetes

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

October 15, 2008

Question: I am hypothyroid and my doctor is treating me with Erfa Throid. I feel better using the Erfa's product. My nurse practitioner says my dose above 1 grain is right for me, but I still have symptoms like sluggishness and a bad memory, dry skin, and I'm too cold all the time. My testing just came back and she said I also have type I diabetes. She told me that my symptoms are from the diabetes. Is there any way to tell whether my hypothyroidism or diabetes is the cause of my symptoms?

Dr. Lowe: I'm sorry you have two hormonal disorders to deal with. Some symptoms of hypothyroidism overlap with some of diabetes. The overlap can confuse the patient and his or her clinician. It may not be clear at all which of the two conditions they need to address to relieve the patient's symptoms. Sometimes, of course, they must address both conditions.

You said your doctor just recently diagnosed your diabetes. Because of this, I assume your diabetes is uncontrolled. If so, you may have symptoms attributable to the diabetes.

Despite that, some of your symptoms are most likely caused by under-treatment for your hypothyroidism. I say this because the 1 grain of Erfa Throid you're taking is too low to provide optimal benefits to most hypothyroid patients. Endocrinologists long ago made the TSH the be-all-and-end-all for deciding hypothyroid patients' thyroid hormone dosages. Before this costly mistake of the endocrinology specialty, patients used higher—and more effective—dosages of thyroid hormone. When they used desiccated thyroid, as you are, effective doses for most patients ranged from 2 grains up to 4 grains.[1][2]

If you're like most patients, then, your effective daily dose will be higher than the 1 grain you're now taking. That will also be your *safe* dose. I say this *emphatically* for one reason—it is *not* safe for clinicians to under-treat hypothyroid patients with thyroid hormone, as most conventional clinicians do nowadays.

Of course, it's important for you to control your diabetes. You hopefully have surviving insulin-secreting beta cells in your pancreas. If so, you stand a good chance of *safely* controlling your diabetes by avoiding anti-diabetic drugs. You can mostly likely do this through diet, exercise, and natural medicine treatments. (Comprehensive information on the natural medicine approach to diabetes is in the 3rd edition of the *Textbook of Natural Medicine*.[3] I highly recommend this book to all diabetic patients and clinicians who treat them.) It will serve you well to go all out in using these methods. If using them controls you diabetes, you can, as I said, avoid anti-diabetic drugs, all of which risk giving you other medical problems.

In general with diabetes, the aim is to maintain a normal blood sugar curve. It's especially important to control the height of your blood sugar rise after eating. This is important because the peak level, if too high, appears to be associate with the most damaging general effects of diabetes.[3] You should monitor your peak sugar levels with what must become (as my wife, Tammy, tells our diabetic patients) your new friend, a glucometer. If money is a concern, Walgreen's TrueTrack glucometer kit is the least expensive on the market; using it and its test strips can save you a great deal of money.

You'll also need to systematically monitor to find your effective dosage of Nature-Throid. At minimum, you should aim at four targets: (1) a basal body temperature between 97.8° and 98.2°F (36.56° and 36.78°C); (2) a basal heart rate in the 70s; (3) freedom from your hypothyroid symptoms and signs; and (4) a sense of well being.

When I say "systematically monitor" in the above paragraph, I mean posting to line graphs at least two sets of measures: (1) your measurements of temperature and heart rate, and (2) the estimated intensity of your symptoms with "symptoms severity scales" twice each week. You can print free of charge both symptoms severity scales and line graphs from our page of evaluation forms; you should use the forms in set 3. (To learn about how to properly monitor, please read chapters 4.3 and 5.2 in *The Metabolic Treatment of Fibromyalgia*.[4])

With a high degree of probability, you can control both your hypothyroidism and your diabetes. To maximize your chances, I urge you to maintain an unyielding commitment to optimal health, insist on truly effective clinical care, and tweak your treatment at intervals based on systematic monitoring. I sincerely wish you the best.

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More On Blood Sugar

| Low Blood Sugar Despite a Complex Carb Diet: Finding It and Fixing It |

Tammy@drlowe.com

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Central Hypothyroidism

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

Latest Updates to drlowe.com

| Problems with T4 replacement |

| Weight gain and the TSH (at *Thyroid Science*) |

Q&As

October 28, 2005
Question: I have some of the hypothyroid symptoms you list on your website. They aren't severe but they're strong enough to be annoying. I have a very healthy lifestyle, take vitamins, and exercise every day. Because of that, I disagree with the doctors who've told me that my symptoms are lifestyle related. Several doctors have tested me for hypothyroidism. My T4 and T3 levels are in the lower part of the normal range, but my TSH is always low. The doctors tell me I shouldn't take thyroid hormone because my TSH shows that I'm hyperthyroid. If that's true, why do I have symptoms of the opposite condition, hypothyroidism?

Dr. Lowe: Hyperthyroid patients do have low TSH levels, but a low TSH definitely does *not* always mean that a patient is hyperthyroid. In fact, despite your low TSH, you may be hypothyroid. If so, that will explain your hypothyroid symptoms.

We see this lab test pattern among patients who have "central hypothyroidism." In this disorder, the patient has a thyroid hormone deficiency *because* her TSH is low. The TSH is low because of a problem with either the hypothalamus or pituitary gland.[1][2][3][4][5][6] The hypothalamus normally sends the hormone TRH to the pituitary gland, stimulating it to secrete TSH. TSH then passes through the blood to the thyroid gland and stimulates it to secrete the thyroid hormone. But if the hypothalamus or pituitary gland dysfunctions for some reason, too little TSH may be secreted to properly regulate the thyroid gland. If so, the patient may have low or low-normal thyroid hormone levels, and her TSH level will also be low. An understanding of central hypothyroidism makes it clear that we can't rule out hypothyroidism based on a low or low-normal TSH level.

We've had many patients with central hypothyroidism who suffered for years because their doctors falsely believed that their low TSH levels meant they were hyperthyroid. The doctors ignored the fact that the patients had clear-cut symptoms and signs of hypothyroidism.

Incidentally, that your symptoms aren't severe but are mild or moderate is consistent with central hypothyroidism. As a group of Italian researchers pointed out, the symptoms and signs of patients with central hypothyroidism are usually milder than those of patients with "primary hypothyroidism" (thyroid hormone deficiency due to a problem with the thyroid gland itself).[7]

In your circumstance, I think the best course of action is to get your resting metabolic rate measured. If it's abnormally low, factors other than hypothyroidism may account for it. For example, calorie restriction, a testosterone deficiency, or lose of muscle mass may be responsible. If you rule out these and other such factors, then chances are you have central hypothyroidism. It will be useful for you to also undergo other tests to see if the results support the diagnosis. For example, low voltage of the QRS complex on an EKG is consistent with hypothyroidism.

Clearly, for doctors to depend only on TSH levels to rule out hypothyroidism can be a disservice to patients. You may learn that you're among these disserved patients if you follow through with the testing I've suggested.

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April 15, 1998
Question: After reviewing your T3 protocol for fibromyalgia, my endocrinologist agreed to put me on trial of Cytomel at 25ug/day. Six weeks later my fibromyalgia fog was beginning to lift and I could tell I was feeling better, but my TSH test fell to near zero on Cytomel and he took me off for about 2 weeks. My FM symptoms regressed. I convinced him to redo the blood work asked him to include T4, TSH, and T3 to prove to him that I was not "hyperthyroid" on T3. He agreed, and this time he found my T4 and TSH near zero and my T3 very low. He agreed to put me back on Cytomel and retested for T4, T3, and TSH after 3 months. This time both T4 and TSH were nearly undetectable and T3 was normal, but I was beginning to feel much better. Much of my soreness was greatly reduced and most of my tingling (paresthesia) was gone. I was still easily fatigued physically and mentally, but I could tell I was much improved. My chiropractor measured only 3 of 18 FM pressure points! Following this last thyroid test, my endocrinologist said my tests were more consistent with central hypothyroidism and that my TRH stimulation test had only been barely normal, and he put me on full thyroid treatment. Thankfully, my MRI was normal. Remarkably, he agreed to keep me on 25ug Cytomel since I was doing so much better and added 25mg Synthroid. Although these levels are relatively low, I am feeling nearly normal. But, I'd like a little more improvement. At my last blood test a couple of weeks ago my TSH was 0.22, T4 was 1.07, T3 was 157—all indicating my T3/T4 medicine was doing well. My endocrinologist now believes that I have had fibromyalgia/stress induced central hypothyroidism since my pituitary appears to be normal on the MRI and it is functioning normally with regards to its other hormone systems. He's continuing Cytomel and Synthroid and plans to check my blood levels every 6 months for the next couple of years. He then would like to withdraw the T3 and T4. Is it reasonable that I could withdraw and be healed of FM and hypothyroidism? Could my Synthroid and/or Cytomel be increased above 25mg and 25ug without overtreating me into "hyperthyroidism"? Is my T4 of 1.07 "optimal" (T4 test range 0.70-1.85)? Thanks for your help.

Dr. Lowe: It is not likely that your central hypothyroidism was stress-induced. The high incidence of primary and central hypothyroidism in fibromyalgia patients is often dismissed as merely "stress-induced." It is improbable, however, that this mechanism accounts for *long-lasting* fibromyalgia manifested as hypothyroid symptoms—especially when the symptoms last for more than a few weeks. During stress (such as surgery or an auto accident), the adrenal glands increase their secretion of cortisol. The increase in cortisol inhibits the thyroid system in two ways: (1) it decreases TSH secretion by the pituitary gland, and (2) it decreases conversion of T4 to T3. However, these thyroid-inhibiting effects last *only* a few weeks at most. Despite Dr. Dennis Wilson's claim that impaired T4 to T3 conversion becomes "stuck," there is no evidence to justify this speculation. The available scientific studies and my laboratory testing deny that this occurs. Instead, that the thyroid-inhibiting effects of stress are a brief phenomenon has been well-documented. Even when a patient takes cortisol as a medication (such as prednisone) for months, full TSH secretion and conversion of T4 to T3 "recover" to normal within a few weeks. Because of this, it is not likely that "stress" sustained your symptoms over a prolonged time. I would predict that your symptoms would soon return if you were to stop taking exogenous thyroid hormone.

This leads to the question: What may account for your central hypothyroidism? Your normal MRI (presumably of your pituitary gland) rules out structural abnormalities, such as tumors or atrophy of the gland. But your pituitary may fail to synthesize enough TSH because of other abnormalities that cannot be detected by an MRI. For example, gene transcription for TSH mRNA may be impaired, possibly because of one or more mutations of the TSH subunit genes. This would result in abnormally low TSH synthesis and secretion. Verifying such abnormalities is technically difficult now, but such an abnormality would make it likely that you will always have to take thyroid hormone to maintain your improved state.

Regarding your dosage, keep in mind that the point to taking thyroid hormone is to normalize tissue metabolism. Unfortunately, blood levels of thyroid hormones and TSH are not measures of tissue metabolism. They are an assessment of the

Tammy@drlowe.com

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interaction of the pituitary-thyroid gland axis, and nothing more. (This assessment is helpful in diagnosing an untreated patient's thyroid status. It is, however, useless as a gauge for adjusting dosage.) There is no good evidence that the blood levels of these hormones correlate well with tissue metabolism. Because of this, if your goal is normal metabolism, the "optimal" blood levels of T3 and T4 must be determined on an individual basis. This is accomplished by adjusting your dosage so as to provide optimal health without tissue overstimulation. Imposing a predetermined blood level on an individual patient usually results in a poor clinical outcome. The only effective method for most patients is for the clinician to abandon the blood tests altogether and adjust the dosage according to measures of tissue metabolism.

Fibromyalgia: What Is It?

Latest Updates to drlowe.com

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

Q&As

October 12, 2010
Question: Are fibromyalgia and hypothyroidism really linked? I think that they are. I have fibromyalgia and I also have weight gain, although I eat very little and have body swelling and many other symptoms of hypothyroidism. Conventional thyroid lab tests come back as normal, but I know in my gut I have a real thyroid problem. How can I get a more sophisticated, discerning thyroid testing done? I am in the UK? Thank you very much for your time.

Dr. Lowe: Most patients’ fibromyalgia is definitely related to too little thyroid hormone regulation! For those patients, what we call “fibromyalgia” is largely a set of symptoms that develops from too little thyroid hormone regulation. The two essential symptoms are chronic widespread pain and abnormal tenderness. However, the so-called “associated fibromyalgia symptoms”[1,2] are each classic hypothyroid symptoms.

Some patients’ inadequate thyroid hormone regulation occurs because of they have thyroid hormone deficiencies; for others, it occurs because of they have partial cellular resistance to thyroid hormone. In either case, the predominant symptoms can be widespread pain and tenderness. However, many fibromyalgia patients’ symptoms are worsened by lifestyle factors such as nutritional deficiencies and a pro-inflammatory diet, and various prescription drugs.

The “more sophisticated, discerning” tests you ask about are for the most part not laboratory tests, although for some patients, various lab tests can be helpful. But the conventional laboratory thyroid function tests (TSH, free T3, and free T4) are largely useless unless one or more of the levels is way out of range.

The important points are these: In-range TSH, free T3, and free T4 levels simply cannot logically rule out that a patient needs thyroid hormone therapy. And when a patient is undergoing thyroid hormone therapy, these test levels are not accurate gauges of the effectiveness of the therapy.

You said your thyroid lab tests were within range. Because of that, were I you, I wouldn’t waste time undergoing more of the conventional tests. Instead, I would look for a clinician who’ll listen to me, look at me, physically examine me, and do physiological (such as your Achilles reflex speed and the voltage of your ECG/EKG) and limited, meaningful lab tests.

You’ve apparently tried to get an accurate diagnosis from physicians who lack skills at what’s called “pathognomy” (pa thog’ no mē). This term means the study and knowledge of the symptoms and all other characteristics of a disease. The term comes from the Greek for “skilled in judging disease.”

When you find a competent physician, he or she will practice pathognomy. Years ago, I invented the term “extremist medical technocrat” during an interview with Mary Shomon. What I meant by this term is that most conventional physicians don’t practice pathognomy; instead, they practice a extreme medical technocracy. That is, they focus solely on lab test results, stair into their computers screens rather than you without giving you so much as a glance or permitting you to express yourself. In my view, for a physician to fail to embrace and practice pathognomy is to forsake his or her patients, such as you.

Laboratory thyroid function tests tell us nothing whatever about whether a person’s tissue metabolism is sufficient regulated for the person to be healthy. They tell us nothing whatever about a patient's thyroid-hormone-related general metabolic status. Thyroid patient advocates at Thyroid UK are a caring resource for people such as you in the UK. I encourage you to contact them. Their organization’s contact information is at their website: http://www.thyroiduk.org.uk/tuk/index.html

You can learn a great deal about the relation of fibromyalgia to thyroid hormone by reading some of the hundreds of webpages at www.drlowe.com. But I especially encourage you to read a review paper Jackie Yellin and I wrote a couple of years ago for *Thyroid Science*.[3] It the paper, we summarized the evidence that inadequate thyroid hormone regulation is the main underlying factor of most patients' fibromyalgia. It’s likely that seeing the evidence will turn your suspicion that fibromyalgia and thyroid hormone are linked into an steadfast belief.

I hope this reply is helpful to you, and I wish you the best for soon recovering your health.

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September 23, 2002
Question: My endocrinologist said that he doesn't really think that I have fibromyalgia. His reason is that I my fibromyalgia symptoms started suddenly after I injured my neck by turning it too quickly. Have you had any patients whose fibromyalgia symptoms started suddenly after an injury?

Dr. Lowe: According to some studies, about 30% of patients' fibromyalgia symptoms are "post-traumatic." This means that their symptoms began either at once or shortly after a trauma. Obviously, a sudden onset of fibromyalgia symptoms is fairly common.

In *The Metabolic Treatment of Fibromyalgia*, I gave the a plausible explanation for the sudden onset of fibromyalgia symptoms following a trauma. When I carefully scrutinized many patients' medical histories, I came to a tentative conclusion: The typical patient with post-traumatic fibromyalgia symptoms has a history of marginally adequate metabolism. The marginally adequate metabolism is suggested by experiences the patient commonly reports after some contemplation—intermittent hypothyroid-like symptoms, especially after or during physical and emotional stresses.

As a part of stress—either physically or emotionally induced—the adrenal glands release more "cortisol." Cortisol is a hormone that helps the body adapt to cellular needs that abruptly change during stress. The blood cortisol consequently rises. The increased cortisol transiently suppresses the thyroid system. Increased cortisol reaching cells of the pituitary gland suppresses TSH secretion. As a result, the reduced TSH reaching the thyroid gland decreases the glands' release of thyroid hormones into the blood. The increased cortisol reaching other cells inhibits their conversion of T4 to T3. The result is a body-wide slowing of thyroid hormone-driven metabolism.

In most people, the slowed metabolism might not generate fibromyalgia (hypothyroid) symptoms. But some patients’ metabolism was only marginally adequate to start with. Slowing their metabolism even more can induce symptoms typical of hypothyroidism, which doctors diagnose as fibromyalgia. Most clinicians today fail to recognize these symptoms as those of hypothyroidism. This is especially true of most endocrinologists, who over the past 30 years have all but lost the ability to recognized hypothyroid symptoms for what they actually are. Hence, the patient may end up with a diagnosis of post-traumatic fibromyalgia. The correct diagnosis, however, would be hypo-metabolism secondary to post-traumatic hypothyroidism.

It's important to note that if the patient's cortisol level stays high, her thyroid system usually "escapes" the inhibiting effect of the cortisol. The escape usually occurs within a few weeks. But the injured patient, especially if her injury was severe, is likely to be relatively inactive physically for a few weeks. She may even be inactive for a few months. Her low physical activity during this time is likely to reduce her body's muscle mass. The reduction in mass will lower her metabolism even further. Keep in mind: Other factors held constant, our metabolic rate is proportional to our muscle mass. Even a small loss of muscle mass in a patient with marginally adequate metabolism may reduce her metabolic rate enough to produce chronic symptoms of abnormally slow metabolism.

In my experience, many fibromyalgia patients come to realize they've long had symptoms of slow metabolism only after learning what the symptoms are. Their realization often occurs after they've recovered a noticeable degree of metabolic health. Experiencing good metabolic health teaches them to distinguish good from poor metabolic health.

Is this mechanism of post-traumatic fibromyalgia established scientifically? No, it's not. But it's reasonable based on the available scientific evidence, and it’s presently our only plausible explanation. Certainly it deserves investigation. You, of course, are the best person to decide whether the mechanism applies in your case. Regardless, understanding the mechanism can help one to see how some patients’ fibromyalgia symptoms might start after an injury. Perhaps you can share this causative conjecture with your endocrinologist. Perhaps he’ll then appreciate the fact that some patient’s fibromyalgia symptoms are post traumatic and do develop suddenly.

November 5, 2000
Question: My doctor and I are hoping that you will soon solve the problem of fibromyalgia. How much longer do you think it will take?

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Tammy@drlowe.com

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Dr. Lowe: The time has passed. We've already solved the problem of fibromyalgia. In addition, we have a treatment, "metabolic rehabilitation", that relieves some 75% to 85% of patients from their fibromyalgia symptoms—fully and permanently. I explain the solution and the treatment succinctly on various pages of drlowe.com, and I explain in depth in *The Metabolic Treatment of Fibromyalgia*. In a single statement, fibromyalgia is the symptoms and signs of too little thyroid hormone regulation of tissues, due either to hypothyroidism or thyroid hormone resistance, complicated in most cases by a health-impairing diet, nutritional deficiencies, and physical deconditioning.

But it isn't enough that we've solved the scientific problem of fibromyalgia. We must now solve a daunting psychosocial problem—how to educate other fibromyalgia researchers and practicing doctors about the fact that we've solved the problem. This educational undertaking is proving far more difficult than solving the scientific problem. The main difficulty is the unscientific code of conduct that predominates in conventional medicine. In compliance with this code, most conventional medical researchers and doctors dogmatically cling to false beliefs they've accepted without question while bowing before the throne of medical authority. This unscientific code of conduct is often whitewashed as the "conservative nature of doctors." It is, however, a major obstacle to the relief of human suffering from disease. Tragically, as we toil at this educational task, patients with the set of symptoms we label "fibromyalgia" will continue to suffer on a worldwide scale.

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Weight Gain & T4 Replacement

Latest Updates to drlowe.com

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

Q&As

October 4, 2004

Question: I'm a 32-year-old female who is 5 feet 2 inches tall. I weigh 180 pounds. I had my thyroid removed eight years ago. At that time, I weighed only 140 pounds. For the whole eight years, I've had aches and pains, fatigue, air-headedness, and weight gain. My doctor diagnosed my condition as "depression" and prescribed antidepressants and painkillers. I've been lectured by everyone, my doctor included, that all of my symptoms would be controlled if I'd just lose weight. His diagnosis of depression and all the lecturing has gotten me into the mind set that I'm just fat and lazy.

The doctor has tested my TSH annually and adjusted my Synthroid dose up and down, and even when the dose is up, I still don't lose weight. I've tried every way to lose the weight. I've done the starvation diet and even diet pills. My weight went up and down a little but has never stayed down. I even tried the "no carb" diet for eight weeks with my Mother. She lost 30 pounds and I lost *nothing*! I take nutritional supplements, am on the Zone diet, and joined a gym and work out four times a week, but I'm still not losing weight. Although I work out, I have trouble not feeling that I'm just fat and lazy. I'm now taking 200 mcg of Synthroid. My doctor says that's such a large dose that it rules out hypothyroidism as the cause of my weight problem. Should I consider some other hormone problem?

Dr. Lowe: The "hormone problem" you need to consider is the T4-replacement you're on. A study published in 2000 showed that weight gain is the *usual* result of being on T4-replacement therapy.[1] This confirms what hundreds of patients on T4-replacement have told us: they gained weight on T4-replacement and couldn't lose it, even if they dieted and exercised, and they lost the weight shortly after switching to a slightly TSH-suppressive dose of a T4/T3 product, such as Armour or Thyrolar. These patients weren't fat and lazy when they were on T4-replacement. Instead, they weren't breaking down fats fast enough because T4-replacement was ineffective for them. And most likely, that's exactly why you've gained and retained weight.

I strongly recommend that you read the section titled "Weight Gain" in my recent critique of Dr. Richard Guttler's false beliefs about hypothyroidism. I think you'll benefit by reading the whole section, but pay particular attention to the passages about the "Beckett and Toft" study.

I hope you completely clear your head of the idea that you're just fat and lazy, and I hope you soon lose your excess weight. You can easily do that by finding a doctor who'll switch you from T4-replacement to a safer and more effective approach to thyroid hormone therapy. With your wholesome diet, nutritional supplements, exercise, and more effective hormone therapy, you should in short order lose the weight T4-replacement caused you to gain and retain.

Reference

[1] Tigas, S., Idiculla, J., Beckett, G., and Toft, A.: Is excessive weight gain after ablative treatment of hyperthyroidism due to inadequate thyroid hormone therapy? *Thyroid*, 10(12):1107-1111, 2000.

| Weight gain and the TSH (at *Thyroid Science*) |

| More problems with T4 replacement |

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Female Problems

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

Q&As

February 6, 2003
Question: My body is always in pain, every day. If it isn't my knees, it's my neck or shoulder, low back or mid-back. I go to my chiropractic doctor every week and have for many years. I sleep on a thermo-foam type mattress. But I don't sleep thru the night. My GP prescribes Bextra for my pain from a left knee surgery in 2001. I feel worse when I don't take it, but even with it I feel like an old lady. I'm 47-years-old, and it feels like I'm getting older every day.

I went to an endocrinologist early in 2001 because I wasn't feeling right. My muscles are always tight, memory is poor, my weight is always an issue, and I have extreme fatigue, especially during my menstrual cycle. During my period, I have very heavy blood loss for two days. My first gynecologist did nothing for the heavy bleeding. The endocrinologist did blood work and said I was anemic. He also said that my thyroid was in the low range of normal. This is the same as it has been since my early twenties. He said there was no need for thyroid medication.

I went to another gynecologist in 2002. She told me my anemia is caused by large uterine fibroids. I was on Lupron for six months to shrink the fibroids and to prepare for a hysterectomy. Well, the fibroids barely shrunk and I barely lost weight. So she said I was too high a risk for surgery. In two weeks, I'll undergo fibroid embolization. I hope this stops the bleeding.

Could my problems be related to hypothyroidism? Should I see a rheumatologist, which has been recommended? What do you think?

Dr. Lowe: I'm afraid you've taken a seat on the medical merry-go-round that millions of hapless patients find themselves riding. If you're to get well, you must promptly give up your seat and hop off. That means, of course, giving up conventional medicine.

You wrote that you have chronic pain; tight muscles; poor memory; extreme fatigue, especially during your menstrual cycle; heavy menstrual flow; and anemia. These are classic symptoms and signs of hypothyroidism. They shout out hypothyroidism, and your low-normal thyroid test results amplify the shout.

I've had many hypothyroid women patients over the years who had hysterectomies because of profuse menstrual bleeding. Their medical histories indicated that hypothyroidism was caused. Like you, they had low-normal thyroid function test results and classic symptoms and signs of hypothyroidism, including the profuse bleeding. After the women had undergone hysterectomies, their other hypothyroid symptoms and signs continued to bother or torment them. After spending small fortunes on medical care to control their continuing symptoms, they eventually ended up in my clinic. Then they got the final confirmation that hypothyroidism had caused their heavy bleeding—rapid and full recovery from all their symptoms and signs with proper metabolic therapy.

For a surgeon to stop heavy menstrual bleeding by removing a hypothyroid woman's uterus is like putting tape over the flashing oil light on the dash board of a car. Doing so stops an annoyance. But, as for the car, it's a harmful and costly expedient for the woman.

Embolization, of course, isn't as horrific as a surgeon unnecessarily removing a woman's uterus. During embolization, a doctor introduces a substance into the patient's circulation to occlude blood vessels. This can arrest hemorrhaging when it comes from the area of a fibroid. But if the cause of the heavy bleeding is hypothyroidism, the embolization won't stop the bleeding. To stop it, the doctor would have to embolize the woman's enter uterine lining, That, of course, shouldn't be done because it would then necessitate hysterectomy.

Before undergoing any invasive procedure to stop the heavy bleeding during your period, I suggest you try another option: Find an alternative doctor who'll give you a trial of thyroid hormone therapy with a high-enough dose of a T4/T3 thyroid hormone preparation. Based on my clinical experiences with women with your history, it's highly probable that the therapy will relieve your symptoms and signs. And there's a good chance the therapy will eliminate the need for you to undergo any invasive gynecologic procedure, including embolization.

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Nutrition

Latest Updates to drlowe.com

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

Q&As

April 22, 2007
Question: I was taking vitamins, but I didn't see that they were helping me, so I stopped. I just don't see why you push nutritional supplements so much on your website and in your books. Do you make money off them?

Dr. Lowe: First let me say that unlike many doctors, I have no vested financial interest whatever in *any* nutritional product. Nor do I resort to the ploy that I donate royalties from supplements to charity. I don't sell them or profit from them financially in any way.

That issue aside, I'd like to address an issue that could make all the difference in you being relatively healthy and youthful throughout your life. Many patients have told me they felt much better after they started taking nutritional supplements. I even know of a few people whose fibromyalgia and other hypothyroid-like symptoms ceased after they started taking supplements.

Conversely, many people who begin taking supplement for the first time see no dramatic benefits over night. That seems true for you. That being the case, rather than you abandoning supplements, I encourage you to consider the subtle benefits of taking them.

Take, for example, the reduction of free radicals in your body. These are atoms or molecules that have unpaired electrons in their outer shells. These unpaired electrons make the atoms or molecules extremely reactive. They are so reactive that they set off rapid chain reactions. These destabilize other molecules and produce many more free radicals. Antioxidants available in supplements deactivate free radicals.

Anti-aging experts have long argued that free radicals are the main agents of aging. Reduce your body's free radical content, they argue, and you'll age more slowly and maintain a more youthful appearance, even into old age.

I had the opportunity to witness a case in point when I was in chiropractic college. Once a month, I attended a meeting of a health organization in Los Angeles. Another often attendee was the beautiful silent-movie actress Gloria Swanson. She was an avid health enthusiast. So was her last husband, William Duffy. He wrote the famous book *Sugar Blues*, a *vade mecum* of John Lennon and other anti-sugar advocates. One author wrote, "Gloria was insane about the use of sugar. I mean she would go ballistic if someone used it around her. She claimed that America lost the Vietnam War because of sugar."

Gloria was seventy-five-years-old then, but she was youthful and beautiful enough to hold the attention of most of the men at the meetings—despite the presence of much younger attractive women. Had any of us guys had the chance to leave the meeting with one of the women, it would've been Gloria.

Nutrients such as vitamin C reduce free radicals in our bodies. But while they are doing this, no flashing neon gauge pops into the forefront of our minds with a needle telling us how our free radicals have dropped. We have no *immediately* perceptual gauge that lets us how much we've benefited. But despite that, benefited we indeed have.

What I recommend is that you study credible nutritional literature and come to understand the *subtle* ways that various supplements can help you *over the long haul*. You can get high-quality supplements for a modest price, and ingest them quickly each day. The price and time are well worth many the subtle benefits you're likely to get from them over the years. For example, you may avoid dying of heart disease, and you may stave off cancer. And, at seventy or eighty years old, you may well turn young men's heads the way Gloria Swanson did mine.

March 22, 2006
Question: I read in a book you wrote that taking vitamin C keeps people from having colds and the flu. Since I read that two years ago, I've been taking 250 mg two times a day, and in that time, I've had two colds and the flu once. Why isn't vitamin C working for me?

Dr. Lowe: I don't believe you're taking enough vitamin C, but even if you were taking more, you'd most likely still have colds and the flu on occasion. However, you'd probably have them less often, and when you did, they would likely be less severe.

An effect of vitamin C on disease in general is illustrated by a study published thirty-five years ago.[1] The study included 221 dentists and their wives. The researchers determined how much vitamin C each of the 442 people consumed each day. They also had them fill out the

| Weight gain and the TSH (at *Thyroid Science*) |

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November 2, 2002
Question: I'm being treated—not too successfully—with 0.1 mg of Synthroid (T4) for my hypothyroidism. A couple of months ago, after reading the nutrition section of your website, I began taking nutritional supplements. My hope was that the supplements would make the Synthroid work better. After a couple of weeks, my skin turned a yellow color. My doctor thinks the cause is the carotenes I'm taking as a supplement. He told me the amount I'm taking is small, but he thinks I have a low requirement for carotenes. He said because of that, even the small amount I'm taking has turned my skin yellow. He advised me to stop taking the carotenes. But I've read so much about their health benefits that I'm reluctant to stop taking them. Do you know how I can clear up the yellow color without stopping them?

Dr. Lowe: You may be right that your thyroid hormone therapy probably isn't effective. If so, then the cause of your yellow skin probably isn't a low requirement for carotenes. Instead, it's more likely that your intestinal cells aren't converting carotenes, especially beta-carotene, to vitamin A quickly enough.

Sluggish conversion of carotenes to vitamin A, with yellowing of the skin, is common in a certain class of hypothyroid patients—those who are untreated or under-treated with thyroid hormone. Too little thyroid hormone regulation of intestinal cells slows their metabolism; as a result, the cells convert carotenes to vitamin A much too slowly. The unconverted carotenes enter the blood, raising its level and turning the skin yellow. Because of the slow conversion, even small amounts of carotenes from eating vegetables and fruits turns some patients' skin yellow.

Most doctors will want to make sure that a patient's yellow skin isn't jaundice. Jaundice is a yellowish staining caused by bile pigments, often caused by liver disease. We can usually distinguish jaundice from carotene-induced yellowness by closely examining the patient. Bile pigments cause yellowing of the skin, the membrane that lines the mouth, and the sclera (the dense, white, fibrous membrane that, along with the cornea, forms the outside covering of the eyeball). In contrast, excess carotene turns the skin yellow, but not the inside of the mouth or the sclera. Hence, when the skin is yellow, but the mouth and sclera aren't, the cause is more likely excess carotene.

Your doctor may not remember this method of distinguishing jaundice from carotene-induced yellowness. If not, by reminding him, you may avoid needless lab testing he might otherwise order. But, of course, the conscientious doctor will clear up any lingering doubts by ordering appropriate lab tests.

I've seen many patients with hypothyroidism and thyroid hormone resistance who eliminated their yellow skin. The patient usually did this not by restricting her intake of carotenes, but by using a high enough dose of an effective thyroid hormone preparation. The typical patient I've seen with yellow skin was using T4 alone. She eliminated her yellow skin through two steps: First, she switched to a thyroid hormone product containing both T4 and T3, or one containing T3 alone. Second, she disregarded her TSH level and raised her thyroid hormone dose high enough to rid herself of the yellow skin color. Usually, a dose high enough to clear up the yellow color would suppress the patient's TSH level. At the same time, however, that dose also safely eliminates other hypothyroid symptoms that plagued her while she was using T4 alone.

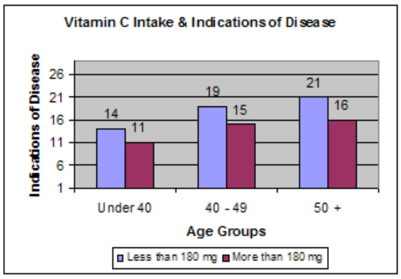
October 24, 2002
Question: I read all over the place that it's important to our health to take omega-3 fatty acids as a nutritional supplement. But I'm confused about this. A popular biochemist on the Internet says that omega-3 fatty acids are bad for the thyroid gland. He says they cause our hypothyroidism to get worse. Do you tell your hypothyroid patients not to take omega-3 fatty acids?

Dr. Lowe: You're not the first person to quote the biochemist and ask whether we discourage hypothyroid patients from taking omega-3 fatty acids. Jackie Yellin and I have searched for the statement by the biochemist you and others refer to, but we haven't found it. If you're quoting him correctly, I don't understand his grounds for the statement. We've found no evidence that omega-3 fatty acids impair the thyroid gland. We have, however, found some evidence suggesting just the opposite—that the fatty acids protect the gland.

Japanese researchers found that among hypothyroid patients, those with higher levels of fatty acids in their blood had less severe hypothyroid symptoms. The also found that patients with lower fatty acid levels had more severe hypothyroid symptoms.[1]

Based on this finding, the researchers suspected that fatty acids

Cornell Medical Index Health Questionnaire. From the Questionnaire, the researchers calculated how many indications of disease each person had. Then the researchers divided the people into two groups: those who consumed less than 180 mg of vitamin C each day, and those who consumed more. Finally, the researchers separated the people into three age groups.



As the graph below shows, older people had more indications of disease. In each age group, however, people who consumed more vitamin C had fewer indications of disease. The researchers weren't specifically studying the effects of vitamin C on colds and the flu, but what they found is relevant to your question: Those who took more vitamin C weren't free from *all* indications of disease; instead, they had *fewer* indications. By extension from the researchers' finding, taking enough vitamin C doesn't mean you'll never have colds or the flu; but you're likely to have milder episodes less often. This is especially true if in your health regimen you maintain multiple preventive practices.

These should include regular exercise, a wholesome diet including black and green tea, and a wide array of nutritional supplements. Among those supplements, of course, should be megadoses of vitamin C.

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somehow enable the thyroid gland to function better despite being impaired. To test their idea, they gave rats a chemical that made them hypothyroid. The chemical damaged the rats' thyroid gland follicles where enzymes assemble thyroid hormones. The chemical also reduced the rats' blood levels of thyroid hormone.

The researchers had some rats that were exposed to the thyroid-impairing chemical also ingest an omega-3 fatty acid. The fatty acid, derived from fish oil, was a purified eicosapentaenoic acid or EPA. Rats who ingested the fatty acid faired far better than the rats that didn't. In rats who ingested the fatty acid, the thyroid-impairing chemical caused less damage to thyroid gland follicles. The rats' thyroid hormone blood levels also remained higher.

The results of this study contradict what you and others say the biochemist claims. Perhaps future studies will contradict the results of this study and show that omega-3 fatty acids harm the gland. Or studies may show that the fatty acids really don't affect the gland at all. For the present, though, I can find no evidence that the fatty acids harm the gland, and only a little evidence (as from the Japanese study) that they protect the gland. The weight of the available evidence—meager as it is—compels us to encourage patients to take omega-3 fatty acids. On another page of drlowe.com, I explain some benefits of these fatty acids and why we recommend their use.

[1] Makino, M., et al.: Effect of eicosapentaenoic acid ethyl ester on hypothyroid function. *J. Endocrinol.*, 171(2):259-265, 2001.

February 6, 2002

Question: I just read a short article by chiropractic nutritionist Dr. G. Douglas Andersen. He described a study in which fibromyalgia patients improved by making diet changes. In the article, Dr. Andersen wrote, "But we are far from a cure." This doesn't jib with what I read on your website site. Can you please comment.

Dr. Lowe: (I read the article by Dr. Andersen, who regularly writes a very helpful column in *Dynamic Chiropractic* updating chiropractic doctors on developments in the field of nutrition. In response to his article, I wrote the following comments to him.)

Dear Dr. Andersen: I appreciate your describing in your article the diet modification that produced positive changes in patients' fibromyalgia status. We have long observed that fibromyalgia patients improve and maintain their improvement only if they make similar diet changes. However, changes in diet alone have enabled precious few patients fully and lastingly to recover from fibromyalgia symptoms. Diet modification is only one component of the approach we call "metabolic rehabilitation." With all the components operating on patients' behalf, the majority fully and lastingly recover from fibromyalgia. By "recover," I mean patients no longer meet the criteria for fibromyalgia, are symptom free, and fully functional—even at 1-to-5-year follow-up.

Many people have never heard of the body of scientific studies that are the foundation of metabolic rehab for fibromyalgia. The reasons for the obscurity are complex. For the most part, though, they involve knowledge-suppressing politics within the fibromyalgia field. A tragic result of the political dynamics is tight control over which studies receive widespread attention by being published in major medical journals. As a result of the control, when most writers outside the fibromyalgia research field, such as yourself, have occasion to write about fibromyalgia, they make statements such as this one by you: "But we are far from a cure; anyone who comes up with the nutritional or pharmacological magic bullet will be able to buy an island and fly there in his or her private jet."

The fact is, whether we call it cure or not, the vast majority of fibromyalgia patients no longer have to remain ill. A first step for them is to wrestle free from the knowledge-suppressing clique of rheumatology fibromyalgia researchers who refuse to consider scientific studies that challenge their prevailing—and false—beliefs about fibromyalgia. Next, since there isn't, and never will be, a magic bullet therapy for fibromyalgia, patients must find a clinician to guide them who is experienced in the complexities of metabolic rehab. This approach is a complex process involving diet changes similar to those you described in your article—but much more. With individualized regimens of rehab, with all the metabolism-improving components operating for the patient's benefit, within two to six months, most patients achieve a metabolic status that frees them from fibromyalgia symptoms and signs. These are not mere anecdotal claims, but conclusions based on analyses of the available scientific evidence. I extend an invitation to you to consider that evidence, much of which is available on drlowe.com.

Q&As

DHEA

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

June 7, 2003

Question: I read your June 6, 2003 answer to another patient who takes DHEA. You wrote that you can't conclude that DHEA will lower a patient's cortisol level. But I've been reading Dr. Barry Durrant-Peatfield's book *The Great Thyroid Scandal and How to Survive It*.[1] On page 99, he explains how DHEA lowers the cortisol level. How do you reconcile that your opinion is different from his?

Dr. Lowe: You've misunderstood the statement by Dr. Durrant-Peatfield on page 99 of his book. Dr. Durrant-Peatfield, of course, is extremely knowledgeable about cortisol and DHEA, and his statement on that page—like the content of his entire book—is clear, which this is one of many reasons that I strongly recommend the book to patients. Despite its clarity, however, I can see how you might misinterpret the statement.

Inside the cells of the adrenal cortex is an enzyme that's dependent on the vitamin panthothenic acid. When cholesterol enters the adrenal cells, this enzyme converts it to pregnenolone. Dr. Peatfield explains quite correctly that pregnenolone is the "pro-hormone" of the adrenal cortex. This means that it's the hormone from which all the other hormones of the adrenal cortex are derive.

Some of the pregnenolone is converted to cortisol. But some patients' adrenal cortex cells don't convert pregnenolone to cortisol at a normal rate. As a result, the patients' cortisol levels may decrease. As Dr. Durrant-Peatfield writes, in these patients, the pregnenolone that would have been converted to cortisol may instead be converted to DHEA. This may raise the patients' DHEA levels, and it may increase the ratio of DHEA to cortisol. Researchers have found this pattern—an increased ratio of DHEA to cortisol—in patients with panic disorder.[2]

In summary, cells of the adrenal cortex may use less pregnenolone to produce cortisol, and this may divert more pregnenolone into the pathway that leads to DHEA. If so, lab tests may show a low ratio of cortisol to DHEA. This does *not* mean, however, that DHEA has suppressed the cortisol level. As Dr. Durrant-Peatfield suggests, it simply means that the cells of the adrenal cortex have increased their production of DHEA at the expense of cortisol.

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[2] Fava, M., Rosenbaum, J.F., MacLaughlin, R.A., et al.: Dehydroepiandrosterone-sulfate/cortisol ratio in panic disorder. *Psychiatry Res.*, 28(3):345-350, 1989.

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June 6, 2003

Question: I've read that taking DHEA lowers patients' cortisol levels. My doctor measured my level and said it is borderline low. For several years, I've taken 10 mg of DHEA. This is supposed to be a small dose, but do you think the 10 mg of DHEA is the cause of my borderline low cortisol level?

Dr. Lowe: The question of whether DHEA will lower a patient's cortisol level is interesting. Unfortunately, it's one for which we don't have a definite answer. The reason is that study results are contradictory.

In one study, the cortisol level of healthy older men and women was lower after they took 200 mg of DHEA each day.[1] In another study, though, the secretion of cortisol at night in healthy men didn't decrease after they took a single dose of 500 mg of DHEA.[2] In another study, perimenopausal women took 50 mg of DHEA for three months. Their blood cortisol level was 13% lower at the end of the study.[3] But in still another study, the cortisol level of schizophrenic patients taking 100 mg of DHEA each day didn't decrease.[4] Also, researchers gave 12 health rhesus monkeys huge amounts of DHEA for eight weeks. The equivalent dose of DHEA for a 150-pound human being would be 4090 mg for the first four weeks and 5114 mg for the second. During the eight weeks, the monkeys' cortisol levels decrease.[5]

With such mixed study results, we simply can't conclude that DHEA will or won't lower a particular patient's cortisol level. To learn whether it will or won't, we must test the patient's cortisol response to DHEA on an individual basis.

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[4] Strous, R.D., Maayan, R., Lapidus, R., et al.: Dehydroepiandrosterone augmentation in the management of negative, depressive, and anxiety symptoms in schizophrenia. *Arch. Gen. Psychiatry*, 60(2):133-141, 2003.

[5] Haffa, A.L., MacEwen, E.G., Kurzman, I.D., et al.: Hypocholesterolemic effect of exogenous dehydroepiandrosterone administration in the rhesus monkey. *In Vivo.*, 8(6):993-997, 1994.

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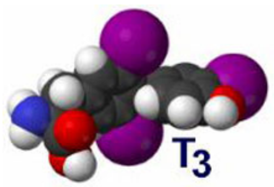
Q&As



T3
(Liothyronine or Triiodothyronine)

Dr. John C. Lowe

Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page and in the right column.

September 16, 2010

Question: Is there a generic version of King's Cytomel in the US? When I began using Cytomel some twenty years ago, pharmacies charged me only about $20 for a month supply. Not they charge me from $120 to $140. I hope there is a generic around.

Dr. Lowe: Paddock Laboratories market a generic T3 product. The link to Paddock's website that your pharmacist may need to reach Paddock: http://www.paddocklabs.com/

As you can see in the picture to the right, Paddock uses the word "liothyronine" on its bottles. The company can't use the term Cytomel® because that word is the registered trademark of King, as the "R" in the little circle after the name signifies. At the Paddock's website's search engine, you'll need to type in the word "Liothyronine" to find the product If you use Paddock's T3 product, let us know how you do with it.

July 12, 2010

Question: I'm perplexed. You say that T3 can be taken alone without T4, but my endocrinologist insists that our bodies absolutely must have T4 along with T3. He says quite emphatically that without T4 in the mix, I won't get the full benefits of my thyroid hormone therapy.

Dr. Lowe: I respectfully disagree with your endocrinologist. Studies indicate that T4 is of no use to anyone except, figuratively, as a storage unit for the metabolically-active thyroid hormones T3, T2, and possibly T1. When T4 ends its long ride through the circulating blood, it enters cells. There, enzymes convert it to T3, and, after a while, other enzymes convert T3 to T2. The T2 becomes T1, and eventually T1 becomes T0 (T-zero). T0 is just the amino acid backbone(called "tyrosine") with no iodine atoms attached. Because it has no attached iodine atoms, T0 is no more a hormone than is T4.

Rather than being a hormone, T4 is a "prohormone." That means that enzymes have to convert T4 to T3 before T4 benefits us. T4 is no more a hormone than beans in an unopened can are a food. For all practical purposes, canned beans become food only when a can opener frees them so you can eat them. Hence, T4, like canned beans, only *potentially* benefits us, but actually does so only after being freed from its metabolically unusable form.

Your endocrinologist may say that T4 is a gentler way to get T3 into your body. This to me, however, is a specious argument. When taken properly, T3 can effect one as gently as T3 derived from T4.

February 4, 2008

Question: In your book *The Metabolic Treatment of Fibromyalgia*, you seem to demolish Dr. Dennis Wilson's theories. What you say makes sense to me. But what about the fact that lots of doctors, mine included, say they get patients well by using T3 as Dr. Wilson teaches. How do you reconcile on the one hand him being wrong about so much, and on the other hand patients getting well with his treatment?

Dr. Lowe: It is nothing new for people to succeed at practical matters despite not understanding why. An example from another field is Adolf Hitler's economic successes before world war II. (I hasten to add that in using this example, I make no association whatever between Dr. Wilson's beliefs or teachings and Hitler's hideous crimes against humanity. I use the example because it's about the issue of some people succeeding at something and maybe not knowing why.)

Historian John Toland (who lost relatives in the holocaust) wrote, "Hitler's achievements in the first four years [of his regime] had truly been considerable and impressive. Like Roosevelt, he had paved the way to social security and old-age benefits. And, like Roosevelt, he had intuitively divined that the professional economists, whose thinking was hobbled by accepted theory, had little understanding of the depression. Both leaders, consequently, had defied tradition to expand production and curb unemployment."[1,p.403]

Toland then quotes economist J. Kenneth Gallbraith: "That a nation oppressed by economic fear would respond to Hitler as Americans did to FDR is not surprising." Toland inserted, "Perhaps [Hitler] understood economics too little to know what he was doing." Then he quotes Gallbraith again: "But in economics it is a great thing not to understand what causes you to insist on the right course."

Perhaps that's true in economics. But I can't agree that in medicine it's a great thing not to understand why a clinician does the right thing and helps patients. I believe that Dr. Wilson failing to know why his therapy helps some patients is a not so great a thing. The T3 therapy he

Also see:

Doctor Says *"No* patient needs to take T3, and T3 can be dangerous." *My reply to him.*

Endocrinology Specialty's *Presumption* that T3 is dangerous

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In fact, order *any* lab test you want at discounted fees through our arrangement with Direct Labs. Fees for thyroid tests are markedly low. The low fees apply to the TSH, T3, T4, thyroid peroxidase, and thyroglobulin antibodies. Just click below and read the easy-to-follow instructions.

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Protect Your Rights to Natural Health Methods

I urge you to sign up to receive alerts from the Alliance for Natural Health: Alliance for Natural Health.

Some legislators are friends of Big Pharma, and these legislators' actions make it clear that they'll use their influence to try to deprive us of natural methods of protecting our health. If they succeed, we'll be enslaved to Big Pharma's drugs to try to control the illnesses we'll develop from our lost natural health protections.

An example of such a legislator is California's Representative Henry Waxman. As Bette noted, Waxman attempts to sneak anti-dietary supplement legislation deep into the back pages of unrelated legislation. I consider this unscrupulous of him. In my opinion, Waxman's actions are diabolical in their potential harm to US citizens, and we need the Alliance for Natural Health to protect us from this legislator.

You can easily learn of these stealth attacks on our health freedoms and conveniently let your legislators know you oppose them. The weight of the citizenry's opinions have many times blocked insidious actions against our freedoms, such as those Waxman has tried to impose. You can conveniently let your legislators know that you insist on health freedoms by subscribing to the newsletter of the Alliance for Natural Health. Another advocacy group that fights for our health freedoms is Citizens for Health.

Whichever activist group you use to let you know it's time to notify your legislators how you feel about anti-freedom legislation, I personally thank you for taking part.

July 5, 2000

Question: I was on a fibromyalgia discussion group last night. The subject of discussion was patients who have thyroid hormone resistance. Someone posted that you believe plain T3, taken once a day, is more effective than sustained-release T3 for these patients.

recommends does indeed help many patients. Based on his book,[4,p.17] however, he is mistaken about why the therapy helps them.

For example, as I wrote in *The Metabolic Treatment of Fibromyalgia*,[2,pp.844-6] he claims that T3 increases body temperature, and the increased temperature activates enzymes that enable patients to get well. It's true that in a research lab, raising the temperature of a petri dish may increase the activity of some enzymes in it. But inside the human body, the range of temperature changes is generally too small to markedly change the activity of enzymes.

Dr. Wilson has it backward: T3 doesn't Increase enzyme activity by raising the body temperature; instead, it's the other way around: T3 increases gene transcription for enzymes (such as sodium-potassium-ATPase), and the resulting increased enzyme activity raises the body temperature. The enzymes do this by cleaving phosphates off ATP molecules. The cleaving releases the energy that was maintaining the phosphate bonds. About half the energy is used to fuel chemical reactions. The other half is released as body heat.

This may seem trifling, and indeed, the issue of which comes first, increased temperature or enzyme activity, may only be an academic concern. But other issues I believe Dr. Wilson gets wrong have practical implications. For example, I don't believe sustained-release T3 is the best use of T3. The reason? The longer T3 stays in the small intestine, the greater the chance that calcium and other agents in food will bind some of the T3. The binding will then carry the T3 out in the patient's stool, reducing the amount that reaches his blood.

Moreover, Dr. Wilson's idea that the enzyme that converts T4 to T3 gets "stuck"[3,p.2] is entirely without scientific substantiation.[2,p.280] In fact, the relevant research literature shows this notion to be close to the outer realm of possibilities. Directing treatment at a "stuck" enzyme is to therapeutically shot way off target. In contrast, treatment intelligently directed at a target that is truly instrumental in causing a patient's symptoms is far more likely to benefit the patient.

As may be with Hitler's economic successes, Dr. Wilson's treatment protocol enables some patients to get well, although I believe he doesn't know why. Too of many of the mechanisms he proposes are refuted by the research literature. Therefore, I believe that what I wrote of the success of his treatment and the mechanisms by which it does so is consistent. Nonetheless, I appreciate you bringing the seeming inconsistency to my attention.

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November 9, 2005
Question: I am a 41-year-old woman who lives on the east coast. About a year ago, my doctor tested me by your protocol and lab tests. When he and I did a telephone consultation with you, he agreed to put me on Cytomel. I now take 100 mcg per day. I'm doing your protocol as you describe it in *Your Guide to Metabolic Health*. I take vitamin supplements daily and exercise at least three times a week. Since I started the protocol and Cytomel, I've regained my life. I have no more pain, no migraines, no swelling, no tingling, no insomnia, and I'm no longer cold all the time. The list of improvements goes on and on. For example, I've lost 65 lbs. I feel great. I suffered for 10 years of my life without a correct diagnosis, so needless to say, I don't want to go back.

The problem I'm facing is that my TSH is very low and my T3 is high. On occasion, I feel that my heart is pounding or I feel anxious. Other than these symptoms every once in a while, I don't feel overstimulated. But because of these symptoms and the lab results, my doctor wants to take me totally off T3 and send me to a local endocrinologist. I've inquired at the endocrinologist's office and learned that he doesn't believe in using Cytomel or your protocol. What can I do? There must be other options than just taking the Cytomel away completely. I feel good now and live an active lifestyle. I don't want that taken away. Please help. I'm desperate not to go back to the way I was before.

Dr. Lowe: The improvements you describe are typical of what we hear from patients using high-enough doses of Cytomel. Because of your improvements, and because your symptoms of possible overstimulation are occasional, taking you completely off Cytomel seems to me radically improper.

For someone taking 100 mcg of T3, we expect your pattern of lab results—a low TSH and high T3. However, your TSH and T3 levels are irrelevant to whether you're overstimulated or not. Two studies we just completed confirm other researchers findings: these tests are *not* reliable gauges of a patient's metabolic status. Many patients taking T3 have TSH and T3 levels like yours but still have severely low metabolic rates. Their metabolic rates become normal only when they increase their dosages further. Their metabolic rates become normal and they have no detectable overstimulation.

In some cases such as yours, the patient's Cytomel dose may need to be reduced. But symptoms such as occasional heart pounding and anxiety are usually not due to a patient's Cytomel dose. I say this because when Cytomel is solely responsible, symptoms of overstimulation are consistent, not occasional.

However, it's important to consider whether a patient's Cytomel dose is high enough to sensitize her to other stimulating chemicals. (Examples are caffeine in coffee, theobromine and theophylline in chocolate, and ephedrine in cold medicines.) If the Cytomel has excessively sensitized her to such chemicals, then when she consumes them in foods or medicines, she'll experiences transient symptoms of overstimulation. She'll be overstimulated for a few hours, but then the symptoms will disappear. The Cytomel will have also excessively sensitized her to her own adrenaline and noradrenaline. Because of this, emotional arousal or intense exercise might also cause temporary symptoms of overstimulation.

The proper solution to occasional symptoms of overstimulation is to find the causes and correct them. The patient's may have to reduce her Cytomel dosage low enough to relieve excess sensitivity to stimulating chemicals. And she may have to reduce her intake of such chemicals. In general, though, the proper approach is not to take the patient completely off Cytomel—not when it has relieved her troubling and disabling symptoms.

Most endocrinologists subscribe to the practice guidelines of the American Association of Clinical Endocrinologists. When a patient such as you sees one of these endocrinologists, he's likely to take her off T3 and switch her to T4-replacement. As many patients have told us, when an endocrinologist switched them to T4-replacement, they became ill and dysfunctional again. These reports are consistent with studies that

This seems contrary to the belief of Dr. Dennis Wilson. If you believe this, why would plain T3 be more effective?

Dr. Lowe: Whoever posted the statement was right. In my experience, for thyroid hormone resistance patients, sustained-release T3 is a poor alternative to plain T3 taken once per day. We don't have enough evidence to know why plain T3 is more effective.

It is possible, however, that some patients have resistance due to mutations in the c-*erb*A-beta gene. Such mutations would result in a patient having mutant T3-receptors that have a low binding affinity for T3. (We've had gene sequencing on a few of our patients to identify mutations in the gene, but the results were negative. However, we'd have to test many more patients before concluding that mutations in the gene aren't generally involved.) Lab studies have shown that mutant, low affinity T3-receptors properly regulate gene transcription only after they're exposed to saturation amounts of T3. Under normal conditions, T3-receptors aren't saturated, and the use of sustained-release T3 isn't likely to provide saturation. Saturation isn't likely to occur with sustained-release T3 because the T3 enters cells only in small amounts over an extended time. As a result, it's not likely that large enough amounts of T3 will reach the receptors at one time to saturate them. But plain T3 in single doses enters cells in larger amounts. These larger amounts may provide the saturation needed to provoke transcription regulation by mutant T3-receptors. If so, these saturation amounts of T3 may induce waves of transcription that on the clinical level relieve symptoms of hypometabolism.

February 1, 1998
Question: Is there any indication for using a divided dose of T3 in a patient whose resting heart rate is already 100? What heart rate would be considered overstimulation if resting is 100? My before lab values showed a normal TSH with a low T4 and free T3. Thanks.

Dr. Lowe: If your resting heart rate is 100, I believe it is important to determine why before beginning thyroid hormone. Some conditions that cause a high resting heart rate contraindicate taking thyroid hormone. If you have one of these conditions, taking thyroid hormone in divided dosages is not likely to avert adverse effects.

There are several conditions that contraindicate the use of thyroid hormone until they are properly dealt with. One is an adrenal tumor called a pheochromocytoma. The tumor secretes epinephrine (adrenaline) and norepinephrine (noradrenaline). This type of tumor is usually benign. But the increased amounts of these hormones can overstimulate some body tissues, such as the heart. The hormones do this by binding to proteins (called beta-adrenergic receptors) on the cells of the tissues. Taking thyroid hormone increases the population of these receptors on the heart muscle. The increase in the amounts of epinephrine and norepinephrine (because of the tumor) reaching the heart, and binding to the increased population of beta-receptors (because of the thyroid hormone) will speed the heart rate even more. Speeding the heart rate in someone with severe cardiovascular deconditioning can be dangerous. The danger is possible impaired blood flow through the coronary arteries due to fat accumulation. The likelihood of this is high if fat metabolism has been impaired by too little thyroid hormone regulation. As the heart rate speeds up, the increased oxygen demand of the heart may cause ischemia (insufficient blood supply). Ischemia can damage the heart muscle. And in extreme cases, myocardial ischemia is lethal.

Another condition that can predispose one to heart muscle ischemia is severe cardiovascular deconditioning. This is common among fibromyalgia patients. Deconditioning of the heart muscle can reduce the volume of blood pumped out of the heart into the circulation with each contraction. The volume of blood pumped out may be too small to meet the oxygen demand of body tissues. If so, various show the ineffectiveness and potential harm of T4-replacement. The studies show that T4-replacement leaves many patients suffering chronically from hypothyroid symptoms[1][2][3][4][5][6][7] and gaining weight they can't lose through dieting and exercise.[8] The patients are also likely to use more drugs and develop one or more of several potentially-fatal diseases.[9]

Potential harm from T4-replacement has thus been scientifically documented. In view of the risks, you must consider for yourself whether you'll permit your therapy to be changed from Cytomel to T4-replacement. If you decide not to permit it, you can seek out an alternative doctor who understands how ineffective and harmful T4-replacement is for many patients. Alternative doctors are generally more cooperative than conventional doctors, and most of them take the time to learn the cause of troubling symptoms. Because of this, you should be able to find one who'll help you ferret out and correct what's causing your occasional symptoms of overstimulation.

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January 9, 2004

Question: I am a doctor in Australia who uses T4/T3 combinations. I'm aware of four subtypes of T3 receptors, but I cannot find any literature on any T4 receptors. Are there any? If not, then why do we need T4 supplementation rather than just T3 alone? Would appreciate some journal references.

Dr. Lowe: In my book *The Metabolic Treatment of Fibromyalgia*, I refer to thyroid hormone receptors as "T3-receptors." I do so because evidence suggests that it is T3 and not T4 that binds to thyroid hormone receptors on genes within the nuclei of cells. In laboratory tests, T4 does bind to thyroid hormone receptors, but with *far* lower affinity than does T3.

It is debatable, however, whether T4 binds to thyroid hormone receptors in our bodies and exerts metabolic effects. Most thyroid researchers today argue that T4 is a storage form of T3. We believe that T4 exerts metabolic effects only after the enzyme 5'-deiodinase removes the fourth iodine atom from the T4 molecule. Removing the iodine atom, of course, converts T4 to T3.

PubMed (US National Libraries of Medicine) lists many review papers on thyroid hormone receptors. If you go to PubMed and type in the key words "thyroid hormone receptor and review," some 17 pages of abstracts will come up. You can then read the abstracts and find articles that you're interested in. If you have a medical library close to you, it will probably carry some journals that contain the articles.

If you don't have a copy of *The Metabolic Treatment of Fibromyalgia*, I recommend it. In the book, I describe and explain the function of thyroid hormone receptors. I also provide massive documentation for the safety and effectiveness of T3 and T4/T3 therapies as alternatives to the generally ineffective T4-replacement. You may find the documentation of value if you have occasion to defend you're practice of T4/T3 therapy.

You asked, if we don't have T4 receptors, "then why do we need T4 supplementation rather than just T3 alone?" With rare exception, we don't.

No one can rationally defend T4 supplementation on scientific grounds. I say this because the widespread use of T4 supplementation is *not* based on scientific studies that show it to be safer or more effective than the use of T3 alone. Instead, its widespread use is the result of a financial venture between the endocrinology specialty and corporations that profit from sales of the most commonly prescribed brands of T4.

Our long clinical experience shows that in general, patients respond far better to T3 alone than they do to T4 alone. Moreover, our safety monitoring of patients shows that the responsible use of T3 alone is as safe as the use of T4 or T4/T3. By "responsible use," of course, I mean employing the same precautions that are appropriate to the use of any thyroid hormone product.

September 24, 2002

Questions: My rheumatologist treats me for my fibromyalgia with amitriptyline, brand name Elavil. I haven't gotten any better from using this drug for a year. At my last visit with him, I asked him to prescribe T3 so that I can see if your type of treatment helps. He went ballistic! He told me T3 will give me osteoporosis and might make me have a heart attack. He said he never prescribes dangerous drugs and he's not going to start by submitting to patients' requests for T3. He said others have also asked for it. If T3 is so dangerous, why do you have your patients use it?

Dr. Lowe: First, let me clarify an important point: Our treatment protocol does *not* consist solely of patients using T3. Only two groups of our patients use T3. One group is patients who appear to have thyroid hormone resistance. The other group is hypothyroid patients who fail to benefit from desiccated thyroid. Our other patients use desiccated thyroid as *part* of their metabolic rehabilitation regimen. (We don't, of course, waste time any more trying T4 alone; it's too seldom of any use.)

Now, to address your rheumatologist's assertion that T3 is dangerous, and his implication that amitriptyline is not. I think the best way to reply to him is to quote publications that are available to him. In the USA, when patients get their prescriptions filled for T3 (usually the brand Cytomel), the pharmacist usually gives them a leaflet on the product. The leaflet contains the following statement:

"NO COMMON SIDE EFFECTS HAVE BEEN REPORTED with the proper use of this medicine." (Medi-Span, Inc.: Database Version 97.2. Data © 1997.)

regulatory mechanisms will speed the rate of heart contractions. (The increased speed of contractions increases the blood entering the circulation, and this gets more oxygen to the tissues.) The speed of contractions will increase until the demand of tissues for oxygen is met. Someone with a small heart in relation to the body mass will have an even faster heart rate naturally. If this heart-speeding process is occurring, and the individual takes thyroid hormone, the heart rate is likely to accelerate even more. And again, ischemia is a risk if the coronary arteries are partially occluded.

Of course, these two conditions don't exhaust the possibilities. I use them just to illustrate my point—that it is important to determine why your resting heart rate is so rapid before beginning thyroid hormone.

I should also mention that if a patient is taking an antidepressant that prevents the reuptake of serotonin, this alone may account for tachycardia (a heart rate of 100bpm or greater). This isn't a rare reaction in patients. In addition, in some patients the increase in serotonin in the heart causes the coronary arteries to constrict. This is most likely the basis for the increase in the incidence of ischemic heart disease and heart attacks among people using these antidepressants over a prolonged time.

Incidentally, one possible cause of your normal TSH and low T4 and free T3 is hypothalamic hypothyroidism. In this condition, the TSH released from the pituitary gland may have a faulty molecular structure. If so, the TSH, though normal in amount, wouldn't stimulate your thyroid gland to release enough T4 and T3. A laboratory can test your TSH for "bio-activity." If this is the problem, the solution to your low hormone levels is to take exogenous thyroid hormone—but only after learning why your resting heart rate is so rapid.

Tammy@drlowe.com

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December 24, 1997

Question: Dr. Smith recently referred one of his patients back to his primary care physician for a prescription for T3. The physician adamantly refused, saying that T3 was old hat, unstable, and caused strokes. Is there anything in the literature about any relationship between T3 and strokes?

Dr. Lowe: The physician should call a pharmacy and request the leaflet given to patients when they pick up a Cytomel (T3) prescription. The physician would learn, as the patient leaflet on Cytomel explains, "POSSIBLE SIDE EFFECTS: NO COMMON SIDE EFFECTS HAVE BEEN REPORTED with proper use of this medication." Other than Nystatin, he probably will find that no other drug he might prescribe is as free from adverse effects as T3.

I don't know what he means by "old hat." As medications go, T4 has been around a lot longer, and desiccated thyroid even longer. As for stability, T3 is certainly as stable as T4 and desiccated thyroid. Synthroid (the most prescribed form of thyroid hormone) is not more stable than Cytomel. At this time, Synthroid users are being reimbursed millions of dollars, partly because of significant variability in the potency of the product.

And ". . . caused strokes"? If anything, the use of T3 may help *prevent* strokes. I scanned MEDLINE for studies on "T3" and "strokes" published between 1966 and 1997.

This statement makes a fact perfectly clear: When used sensibly, T3 is *extraordinarily* safe among prescribed drugs. When I say extraordinarily safe, I'm comparing T3 with drugs such as the amitriptyline which your rheumatologist prescribes for you. Below is a list of potential harmful effects of amitriptyline. This list comes from the *Physician's Desk Reference*, 53rd edition, Medical Economics Company, Inc., Montvale, 1999, page 3418.

> Some patients took amitriptyline at the same time as monoamine oxidase inhibitors. Some of them had crises of extremely high fever. Some had severe convulsions. Others died.
>
> Patients with cardiovascular disease have had a range of harmful effects from taking amitriptyline. Some had irregular heartbeats, extremely rapid heart rate, and abnormalities of their EKGs. Some had heart attacks and strokes. Patients had altered impulse conduction between the chambers of the heart and heart block. Others had low blood pressure, orthostatic hypotension (which many fibromyalgia patients already have), fainting, and palpitations. Other patients had high blood pressure.
>
> Amitriptyline enhances some patients' response to alcohol, barbiturates, and other central nervous system depressants. If a patient taking amitriptyline drinks excess alcohol, "potentiation may increase the danger inherent in any suicide attempt or overdosage."
>
> In pregnant women, amitriptyline crosses the placenta to the fetus. The children of some mothers who took the drug during pregnancy had harmful central nervous system effects, limb deformities, and delays in development.
>
> The patient using amitriptyline may go into a coma. She may have tremors, trouble coordinating her muscles during movement, confusion, disorientation, delusions, hallucinations, and seizures. She may develop a peripheral nerve disorder with numbness, tingling, and other abnormal sensations in the hands, feet, arms, and legs. She may have abnormal involuntary movements such turning of the head one side. Her speech may be impaired, and she may have problems using language properly. Her ability to concentrate may diminish, and she may become restless, excited, and anxious. She may have insomnia, nightmares, and be drowsy, dizzy, weak, and fatigued. She may have headaches and ringing in the ears.
>
> The patient may also have skin rashes, eruptions of itching skin wheals, sensitivity to light, and edema of her face and tongue. The drug may suppress her bone marrow. Her white blood cell and platelet count may drop, and her eosinophil count may rise. Her skin may hemorrhage, and she may develop hepatitis and jaundice. She may be nauseated and have epigastric distress, vomiting, and anorexia. She mouth may be dry and inflamed. She may have odd tastes and lose her sense of taste. The parotid glands in her mouth may swell, and her tongue may turn black. She may also have diarrhea. Her blood sugar levels may become abnormal, and she might suffer liver failure.
>
> The male's testicles and breasts may swell, and he may become impotent. The female's breasts may swell and her nipples discharge a milky fluid.
>
> The patient may gain weight and her hair begin falling out. She may urinate and perspire too much. On the other hand, she may retain urine, and her urinary tract may dilate. She may be constipated, and her bowel may become obstructed from paralysis of the bowel wall.
>
> The pressure in her eyes may rise. Her pupils may dilate and her vision blur, and the ability of her eyes to adjust to distance may diminish. Some patients have developed a lupus-like syndrome with arthritis with positive tests for ANA and rheumatoid factor.

As you can see, T3 has no reported adverse effects. By contrast, amitriptyline has 88 reported potential harmful effects—not the least of which is death. Let me understate the circumstance as politely as I can: Your rheumatologist seems confused about the relative risks of using T3 and amitriptyline. If so, perhaps your sharing this question and answer with him will clear up his confusion.

April 13, 2002
Question: My doctor has begun using your T3 protocol and is getting good results. Thanks for developing the protocol. I get the idea from Internet news groups that more doctors are now using your protocol. Is this true, and do you have any idea how many doctors are using your T3 protocol?

Dr. Lowe: Thank you for writing and letting me know that your doctor is now prescribing T3. I don't know how many doctors are prescribing T3. I do know, however, that over the last several years, many doctors have begun prescribing it in the United States, Canada, and the United Kingdom. This is good news for patients: As steadily more doctors begin using T3 and seeing good results, the unfounded bad name given T3—mainly by conventional endocrinologists—will be rectified. Contrary to the false belief of most conventional endocrinologists, T3 is harmless when used properly, and it dramatically improves many people's health.

You mentioned our "T3 protocol." It's important to understand that this term is *not* an accurate designation of our protocol. Many people mistakenly believe that our protocol solely involves the use of T3. They do so, I suspect, for a particular reason: About a third of our fibromyalgia patients have thyroid hormone resistance, and these patients improve or recover only with the use of T3—*although they must use T3 within the context of a comprehensive program of metabolic rehab.* How this information translates in some people's minds into our protocol *solely* involving T3 is beyond me.

Most of our fibromyalgia patients have either primary or central hypothyroidism. These patients improve or recover with the use of desiccated thyroid (such as Armour)—*but, again, only when they use desiccated thyroid within the context of a comprehensive program of metabolic rehab*.

I'll be grateful if you'll relate this to your doctor so that he'll have an accurate understanding of what our protocol involves. Thank you again for writing, and best of luck with your treatment.

January 30, 2002
Question: I'm a physician who has just begun using T3 in my practice. One thing I'm concerned about is the short half-life of T3. Shouldn't patients divide their daily dose up and take part of it at least twice each day, or instead use sustained-release T3? It seems that this would allow the effects of T3 to continue through the day rather than stop midway or in the evening?

Dr. Lowe: The short time that T3 is in the circulating blood isn't the limit of its beneficial effects on the body. When T3 binds to T3-receptors on genes, the binding regulates the transcription of mRNAs, and the mRNAs are later translated into proteins. The transcription and translation initiated by the binding of T3 to T3-receptors occur in waves, and these waves far outlast the T3 that started them at the chromosomes. Moreover, the newly synthesized proteins themselves far outlast the transcription and translation. As a result, a single dose of T3 will be long gone from the patient's system before he or she experiences most of the benefits of that dose—a molecular and metabolic yield that may smoothly spread out over one to three days. The "rocky road" (
August 7, 2001
Question: During nine months of being very sick, I went through several doctors. Then I read your contribution about T3 in Mary Shomon's book, *Living Well With Hypothyroidism*. Soon after, I found a doctor who agreed to try your treatment. It worked. We started off with 25 mcg of Cytomel and worked our way up until I felt normal. The effective dosage was 125 mcg. I now take 125mcg of T3 in a time-released capsule (75 mcg in the morning and 75 mcg at night). I have been feeling great! However, my doctor is now afraid that we're masking another problem, and he's dropping my dose way down. I wanted your advice since it was truly you who was able to end my being sick.

These key words were mentioned in 43 publications. Most publications reported the *beneficial* effects of T3 on cardiovascular function. The word "stroke" was most often used in regard to the "stroke work in cardiac contractility" (a physiological description)—not in the sense of cerebrovascular accidents (strokes). I'll mention just a few representative publications. These suggest that it is urgent for the physician you mention—for his patients' welfare—to quickly update his knowledge.

In one study, a researcher found that T3 levels were significantly lower in 42 of 65 stroke patients. [Liang, D.S.: Stroke and thyroid hormones. *Chinese Journal of Neurology & Psychiatry*, 24(6):352-354, 384, Dec., 1991] It is certainly possible that the low levels of T3 were partly responsible for the strokes. It is well-known that low thyroid hormone levels result in high blood fat levels, and high blood fat levels predispose patients to heart attacks and strokes. By lowering blood fat levels, the use of T3 is likely to help prevent, rather than cause, strokes in some of the above-mentioned physician's patients.

The use of T3 is even beneficial in patients with the most frail heart conditions. Researchers in one study reported, "Triiodothyronine [T3] administration in patients undergoing cardiopulmonary bypass surgery is safe, may lessen the need for pharmacological (vasodilator) therapy, but may increase heart rate." [Vavouranakis, I., et al.: Triiodothyronine administration in coronary artery bypass surgery: effect on hemodynamics. *Journal of Cardiovascular Surgery*, 35(5):383-389, Oct., 1994]

In rabbits recovering from post-ischemic heart damage, T3 enhanced recovery without adverse effects such as excessively forceful heart contractions. [Wechsler, A.S., et al.: Effects of triiodothyronine on stunned myocardium. *Journal of Cardiac Surgery*, 8(2 Suppl):338-341, Mar., 1993]

In another study, researchers induced severe ischemic heart injury in rats. T3 was administered to some but not other damaged rats. They wrote, "We conclude that administration of T3 in a severe left ventricular injury model significantly augments rapid ventricular recovery." [Salter, D.R., et al.: Acute severe post-ischemic myocardial depression reversed by triiodothyronine. *Annals of Thoracic Surgery*, 54(2):301-305, Aug., 1992]

As I said, these are only a few representative publications. I could cite many other studies that show the opposite from what the above-mentioned physician believes. Every physician has an ethical responsibility to stay abreast of the scientific evidence related to any medical issue he or she renders judgment on. I would urge this physician to live up to this responsibility and use MEDLINE to read the relevant studies. He will learn that rather than causing strokes, T3 is more likely to prevent them. If he doesn't do this, and correct his beliefs about T3, he himself may be responsible for causing in some of his patients the very harm he fears T3 will do.

December 17, 1997
Question: I've been told that you are about to participate in some studies to test the effectiveness for fibromyalgia of the Wilson's syndrome protocol. The point, it seems, would be to see if cycling with timed-release T3—with the eventual goal of "getting off" T3—would alleviate fibromyalgia symptoms without the side effects usually seen with full-strength, one-time-a-day doses of Cytomel. If this is true, why then does your protocol seem to specify only one full dose of non-timed-release Cytomel? And also, if a person can get off the T3, do you believe the cycling will "cure" the resistance?

Dr. Lowe: This is the first I've heard of my presumed participation in a study of Dr. Dennis Wilson's treatment protocol. I would decline to participate for several reasons.

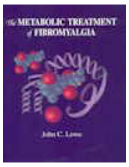
First, the belief that timed-released T3 is of any advantage over plain T3 (such as Cytomel) is simply false. My understanding of the processing and action of T3 in the body leaves me without a plausible explanation of

Obviously, I don't want to mask another problem, but I don't want to go back to the way I was before. I couldn't do anything from work to working out. Please let me know your thoughts on this matter. I greatly appreciate your help.

Dr. Lowe: Congratulations on recovering with the use of T3. I hope your doctor will continue to cooperate and treat you with the dosage of T3 that has proven effective for you. Your having done so leaves me without an idea what your doctor is referring to as another problem masked by the T3.

Your doctor is correct, but only in trifling way. Logically, when someone gets well with the use of T3, we can't conclude that the T3 has relieved a thyroid hormone deficiency or thyroid hormone resistance. With most patients, we only presume that thyroid hormone deficiency or resistance is the mechanism that was causing the health problems that T3 relieved; and we only presume that T3 has corrected a deficiency or overridden resistance. It is within the realm of possibility—but the realm's outermost hinterland—that the T3 may be compensating for some other problem that was causing the patient's symptoms.

Most patients, though, are pragmatic; their main concern is getting and staying well—not remote theoretical possibilities. They are likely to ask, "If my use of T3 isn't harming me, what difference does it make if the T3 is compensating for some other problem?" Again, I'm afraid, the answer is theoretical: T3 could be compensating for some stealthy, progressive, disease-causing process that might eventually make the patient ill or kill her. If so, then the responsible and humane course of action would be to learn what the problem is and properly deal with it; to merely compensate for it with the use of T3 would been irresponsible and inhumane.



The Metabolic Treatment of Fibromyalgia
by Dr. John C. Lowe
Readers' Comments

But you wrote that before beginning the use of T3, you "went through several doctors." I assume that these doctors did diagnostic testing to rule out other health problems and found nothing. If this is true, it seems unlikely that further diagnostic work will unearth problems the T3 could be effectively compensating for. If so, to me, it seems imprudent for you to become ill again (by reducing her T3 dosage) just for a theoretical possibility that T3 may be compensating for another health problem. Besides, I can't think of an underlying condition that T3 might be compensating for that your doctor should be concerned with.

Your doctor and you might also consider another possibility. If you do have some other health problem that T3 is effectively compensating for, T3 might be the proper treatment for that health problem. The T3, by compensating for the other health problem, might in fact prevent the other problem from causing you harm over the long haul.

March 12, 2001
Question: My doctor will only prescribe Synthroid for my hypothyroidism. This medication doesn't seem to work for me because I still have all my hypothyroid symptoms. I asked him to let me also use Cytomel. He refused and said that Cytomel is extremely dangerous. What is so dangerous about Cytomel?

Dr. Lowe: When used properly, Cytomel is not dangerous. Your doctor is misinformed.

Synthroid contains the form of thyroid hormone called T4. Many hypothyroid patients, such as you, benefit little or none from its use, despite the brand they use. Cytomel contains the more metabolically active form of thyroid hormone called T3. T3 is effective for many patients who failed to benefit from the use of T4.

Your doctor's false belief about the use of T3 isn't unusual. Many doctors believe that T3 is dangerous. When pharmacists fill prescriptions for Cytomel, however, they often give patients a leaflet that makes the safety of T3 perfectly clear. Verbatim, the leaflet reads: "NO COMMON SIDE EFFECTS HAVE BEEN REPORTED with the proper use of this medicine." (Medi-Span, Inc.: Database Version 97.2. Data © 1997.) When used with reasonable precaution, T3 is perfectly safe.

Doctors commonly prescribe a variety of drugs to control hypothyroid symptoms that continue despite patients' use of T4. In stark contrast to T3, most of these drugs have long lists of potentially harmful effects. The safety of T3 use starkly contrasts with the risks of using the other drugs. Since this fact is well documented in the medical literature, I find it baffling that so many doctors falsely believe just the opposite.

November 19, 2000
Question: This past week, I talked with my endocrinologist about letting me use T3. She has read information I gave her from your website and commented that it is interesting. However, she is wary of patients using T3 and advised me against using it. I am wondering why you aren't uneasy about recommending T3 when my endocrinologist is?

Dr. Lowe: I am comfortable advising physicians on the use of T3 because of my knowledge of the hormone and my experience (both clinical and experimental) with its use. Moreover, my book The Metabolic Treatment of Fibromyalgia is a comprehensive text on thyroidology and contains more scientific information on the use of T3 than any other book ever written. In contrast, most conventional endocrinologists have little to no knowledge of T3. Also, they have little to no clinical experience with its use. Therefore, for them to represent their opinions about T3 as expert advice is a pretense and raises ethical questions.

Conventional endocrinologists' lack of knowledge about T3 results from conduct that is clearly unscientific—that is, overall, they *accepted without question* mandates passed down to them by old guard thyroid specialists, much as loyal military personnel obediently and unquestioningly comply with orders from higher command. The particular mandate of conventional thyroid specialists I refer to here is this: "The only thyroid hormone preparation a doctor should ever prescribe is T4 (thyroxine)."

To the discredit of both conventional endocrinologists and the thyroid specialists whose edicts the obey, this mandate is *not* scientifically based. Instead, it's based on a powerful marketing campaign of a major pharmaceutical company. This marketing campaign, not science, is precisely why most doctors robotically write "Synthroid" on their prescription pads when they learn that a patient is hypothyroid. Conventional doctors, including endocrinologists, have allowed their minds to be utterly subjugated by this marketing campaign. As a result, they've deprived themselves of clinical experience with any thyroid preparation other than T4.

So, the wariness of conventional doctors, including endocrinologists, about the use of T3 is born of ignorance. Thus, as a whole, they are the least qualified doctors from whom to seek expert advice about T3. In the past several years, many *unconventional* doctors have acquired extensive experience with the use of T3. These doctors include many family physicians, physiatrists, psychiatrists, nutritional and holistic doctors, and naturopathic physicians. For expert advice about T3, it seems prudent to bypass endocrinologists and to look to these more knowledgeable and experienced doctors.

November 10, 2000
Question: I have fibromyalgia and normal thyroid test results. I am on a very good diet and

how timed-release T3 might be superior. Some physicians have told me that timed-released T3 ". . . avoids the cardiac arrhythmias caused by plain T3." My response is that I've done hundreds of series of ECGs on patients taking plain T3, but I've never seen such arrhythmias. (See "Important Issues") The argument that the use of timed-release T3 avoids arrhythmias is a theoretical notion without objective substantiation (there are no studies that show this!).

Second, I don't believe that "cycling" is a valid concept. Over the years, I've monitored scores of fibromyalgia patients who reduced their dosages after improving with the use of T3 (within the context of our entire protocol). Invariably, their symptoms and signs soon became as intense as before they had improved. When they increased their dosages again, they improved again. And once more, when they again reduced their dosages, their symptoms and signs intensified. In many cases, the patient's status worsened after a minor dosage decrease, and improved after a minor increase. The blinded controlled studies we have conducted of fibromyalgia patients taking T3 have involved "cross-overs." This means that without the researchers or patients knowing when, the patients were switched from T3 to placebos and back again. The studies showed clearly that in general, when patients were taking T3, their status improved, and when taking placebos, their status worsened.

These clinical and experimental findings argue against that idea of "cycling" enabling patients to maintain improvement after stopping their use of T3. With increases and decreases in dosage, the only thing that has cycled in our patients is their fibromyalgia status. So, do I believe that "cycling" will "cure" cellular resistance to thyroid hormone? Unequivocally, no!

Third, the leaflet on Cytomel pharmacies give patients when they fill their prescriptions states, "POSSIBLE SIDE EFFECTS: NO COMMON SIDE EFFECTS HAVE BEEN REPORTED with proper use of this medication." This information is accurate—when plain, full-strength, one-time-per-day doses of T3 are used *properly*, there are no adverse effects. The only adverse effects occur when a patient takes a dosage that for her is excessive. With Cytomel, if overstimulation occurs, it can be stopped with one or two small doses of propranolol. Or the patient can simply reduce her dosage of Cytomel the next time she takes it. *I want to emphasize, however, that when our protocol is used properly, there is no overstimulation to be avoided by using timed-release T3. The protocol has safeguards against adverse effects.*

And finally, why do I specify that the typical patient use one full dose of non-timed-release Cytomel for life? Because extensive testing has shown that this is safe, effective, and most economical—when used within the context of our entire protocol.

exercise regularly, as you advise patients to do. Based on your work, my doctor is treating me with T3. But rather than the plain T3 you recommend, he is treating me with timed-released T3. He is convinced that timed-release T3 is the best way since he believes that Cytomel (plain T3) is "a very bumpy road." My question is this: Can a fibromyalgia patient with normal thyroid test results recover taking 125 mcg of timed-release T3? Thank you for your time and consideration.

Dr. Lowe: It is possible that a fibromyalgia patient with normal thyroid test results can recover with the use of timed-release T3. However, the likelihood of recovery is far less than with the use of plain T3. Your normal thyroid test results suggest that your fibromyalgia symptoms are the result of partial cellular resistance to thyroid hormone. For most patients with thyroid hormone resistance, timed-release T3 doesn't work well, if it works at all.

This past year, several Internet doctors, who give advice on thyroid hormone therapy, sired a false belief about the effects of plain T3 on the body—that it causes "physiological instability." These doctors must have a large audience. I say this because I've heard (through e-mails, letters, and phone calls) echoes of their false belief in almost every conceivable variation of words. Your doctor's belief about plain T3 being "a very bumpy road" is an especially creative and graphic variation of the false belief.

Let me explain the error in the Internet doctors' thinking. Within a couple of hours after a patient ingests a single daily dose of plain T3, the blood level of T3 peaks. The Internet doctors infer that because the blood level of T3 peaks, the metabolic reactions of body tissues also peak, resulting physiological instability. Their inference is wrong.

The origin of the doctors' erroneous thinking may be the reaction of the heart to T3 in some individuals. In some patients who take a single daily dose of plain T3, the heart rate slightly speeds up for a short time. The speed up results from a direct effect of the T3 on heart cells. Avoiding this increase in heart rate in patients with fragile heart conditions is prudent. However, in the vast majority of patients, the increased heart rate is transient and harmless. This is especially true for patients who take heart-protective nutrients and engage in regular cardiovascular exercise. (I have written more on drlowe.com about the effects of T3 on heart function.)

In contrast to the heart in some individuals, most other body tissues don't react to plain T3 with a metabolic surge. Certainly, plain T3 doesn't cause physiological instability. Recently, I explained the biological systems that buffer the physiological effects of plain T3, preventing physiological instability. I encourage your physician and you to read this explanation. I hope the explanation will make one thing clear: that overall, only two reactions of the body to plain T3 might, by a stretch, be interpreted as physiological instability: (1) the short-lived peak in the blood T3 level, and (2) a slight speed up of the heart rate. In most patients, neither of these is of any clinical importance.

My research group has spent the past ten years studying fibromyalgia caused by thyroid hormone resistance. We have laboratory proof that about one third of the fibromyalgia patients we've evaluated and treated have thyroid hormone resistance. Our treatment results have forced us to a firm conclusion: For most fibromyalgia patients with thyroid hormone resistance, using plain T3 (as part of comprehensive metabolic rehab) is the *only* route to recovery. With the proper use of plain T3, 75% to 85% of these patients permanently recover. It will be tragic indeed if, despite our research findings, some resistance patients are blocked from taking this route to recovery by a well-intended but false idea that plain T3 is "a very bumpy road" to travel.

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Conversion of T4 and Reverse T3

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

Latest Updates to drlowe.com

Q&As

April 12, 2000
Question: Mary Shomon recommended your website for information on problems with the conversion of thyroid hormone. I have most of the symptoms on a checklist for hypothyroidism. Interestingly, two doctors told me that some of my symptoms are fibromyalgia, but they don't know the cause of my other symptoms. To me, all the symptoms could be hypothyroidism or the problem converting T4 to T3 that Dr. Dennis Wilson writes about. Hypothyroidism is common in my family. However, my doctor has ordered TSH and T4 levels twice, and both times the levels were normal. Since my lab tests are normal, does this mean my "hypothyroid"symptoms are caused by a conversion problem?

Dr. Lowe: No—the clinical picture you describe (normal TSH and T4 levels in someone with hypothyroid-like symptoms) does not necessarily point to a problem in converting T4 to T3. In fact, it is highly unlikely that impaired conversion is the problem. Instead, you may be hypothyroid despite normal TSH and T4 test results. Bear in mind the definition of hypothyroidism: lower-than-normal blood levels of thyroid hormone due to an underactive thyroid gland. Our TSH and thyroid hormone levels vary during the day and from day-to-day during the week. It's possible that when you were tested, your TSH and T4 levels were within the normal range, but that the levels are abnormal at other times. As a result, on average, your tissue may have too little stimulation by thyroid hormone. Also, recent evidence suggests that the so-called "normal" ranges may be too wide. As a result, some people's doctors may believe their test results are normal when in fact the patients are hypothyroid.

In addition, you might have central hypothyroidism. In central hypothyroidism, the thyroid gland is underactive. As a result, the blood level of thyroid hormone is too low, at least part of the time. But the cause of the underactive thyroid gland and low thyroid hormone level is not an abnormality of the thyroid gland. Instead, the cause is a dysfunction of the pituitary gland or hypothalamus. When a patient's standard thyroid test results are normal, the doctor should always consider the possibility of central hypothyroidism. The best way to test for this form of hypothyroidism is the TRH stimulation test. With this test, we identify many patients who're hypothyroid, although their standard thyroid test results are normal.

Some patients do have impaired conversion of T4 to T3. However, the available scientific evidence suggests that at the longest, impaired conversion lasts only a few weeks. I know of no scientific evidence supporting Dr. Dennis Wilson's speculation that some patients have chronically impaired conversion of T4 to T3. When patients have impaired T4 to T3 conversion, they also have a predictable pattern of lab test results. However, despite extensive testing, one other researcher and I have never found this predictable lab test pattern in fibromyalgia outpatients.

Tammy@drlowe.com

Our Educational Consulting Service

We provide educational consulting to both patients and clinicians. Phone us at 603-391-6061, or preferably, write to us at Tammy@drlowe.com. Our fax number is 303-496-6200. —***Tammy Lowe***

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| Weight gain and the TSH (at *Thyroid Science*) |

| Conversion of T4 to reverse T3: Summary |

Continued from bottom of left column . . .

March 24, 1999
Question: In reading your Web site and published articles, I see that you have not paid attention to high reverse-T3 as a cause of thyroid hormone resistance in fibromyalgia. Why have you and other fibromyalgia researchers not given attention to high reverse-T3 as a cause of fibromyalgia?

Dr. Lowe: Some readers will not be familiar with reverse-T3, and I know from experience that many others harbor misconceptions about the molecule. Because of this, I have summarized in the box below what we know about reverse-T3. I've answered your question below the summary.

Conversion of T4 to T3 and Reverse-T3: A Summary

The thyroid gland secretes mostly T4 and very little T3. Most of the T3 that drives cell metabolism is produced by action of the enzyme named 5'-deiodinase, which converts T4 to T3. (We pronounce the "5'-" as "five-prime.") Without this conversion of T4 to T3, cells have too little T3 to maintain normal metabolism; metabolism then slows down. T3, therefore, is the metabolically active thyroid hormone. For the most part, T4 is metabolically inactive. T4 "drives" metabolism only after the deiodinase enzyme converts it to T3.

Another enzyme called 5-deiodinase continually converts some T4 to reverse-T3. Reverse-T3 does not stimulate metabolism. It is produced as a way to help clear some T4 from the body.

Under normal conditions, cells continually convert about 40% of T4 to T3. They convert about 60% of T4 to reverse-T3. Hour-by-hour, conversion of T4 continues with slight shifts in the percentage of T4 converted to T3 and reverse-T3. Under normal conditions, the body eliminates reverse-T3 rapidly. Other enzymes quickly convert reverse-T3 to T2 and T2 to T1, and the body eliminates these molecules within roughly 24-hours. (The process of deiodination in the body is a bit more complicated than I can explain in this short summary.) The point is that the process of deiodination is dynamic and constantly changing, depending on the body's needs.

Under certain conditions, the conversion of T4 to T3 decreases, and more reverse T3 is produced from T4. Three of these conditions are food deprivation (as during fasting or starvation), illness (such as liver disease), and stresses that increase the blood level of the stress hormone called cortisol. We assume that reduced conversion of T4 to T3 under such conditions slows metabolism and aids survival.

Thus, during fasting, disease, or stress, the conversion of T4 to reverse-T3 increases. At these times, conversion of T4 to T3 decreases about 50%, and conversion of T4 to reverse-T3 increases about 50%. Under normal, non-stressful conditions, different enzymes convert some T4 to T3 and some to reverse-T3. The same is true during fasting, illness, or stress; only the percentages change--less T4 is converted to T3 and more is converted to reverse-T3.

The reduced T3 level that occurs during illness, fasting, or stress slows the metabolism of many tissues. Because of the slowed metabolism, the body does not eliminate reverse-T3 as rapidly as usual. The slowed elimination from the body allows the reverse-T3 level in the blood to increase considerably.

In addition, during stressful experiences such as surgery and combat, the amount of the stress hormone cortisol increases. The increase inhibits conversion of T4 to T3; conversion of T4 to reverse-T3 increases. The same inhibition occurs when a patient has Cushing's syndrome, a disease in which the adrenal glands produce too much cortisol. Inhibition also occurs when a patient begins taking cortisol as a medication such as prednisone. However, whether the increased circulating cortisol occurs from stress, Cushing's syndrome, or taking prednisone, the inhibition of T4 to T3 conversion is temporary. It seldom lasts for more than one-to-three weeks, even if the circulating cortisol level continues to be high. Studies have documented that the inhibition is temporary.

A popular belief nowadays (proposed by Dr. Dennis Wilson) has not been proven to be true, and much scientific evidence tips the scales in the "false" direction with regard to this idea. The belief is that the process involving impaired T4 to T3 conversion—with increases in reverse-T3—becomes stuck. The "stuck" conversion is supposed to cause chronic low T3 levels and chronically slowed metabolism. Some have speculated that the elevated reverse-T3 is the culprit, continually blocking the conversion of T4 to T3 as a competitive substrate for the 5'-deiodinase enzyme. However, this belief is contradicted by studies of the dynamics of T4 to T3 conversion and T4 to reverse-T3 conversion. Laboratory studies have shown that when factors such as increased cortisol levels cause a decrease in T4 to T3 conversion and an increase in T4 to reverse-T3 conversion, the shift in the percentages of T3 and reverse-T3 produced is only temporary.

To answer your question: In a 1994 article, I did write of my testing of fibromyalgia patients for laboratory evidence of elevated reverse-T3.

[Lowe, J.C., Eichelberger, J., Manso, G., and Peterson, K.: Improvement in euthyroid fibromyalgia patients treated with T3. J. Myofascial Ther.,1(2):16-29, 1994.] During one year, I tested 50 fibromyalgia patients to see if they had laboratory values that would suggest that they had impaired conversion of T4 to T3 with elevated reverse-T3. I've also tested other patients since 1994. However, I have not found laboratory evidence of impaired T4 to T3 conversion in a single patient.

Also, if impaired conversion was the source of the problem in my fibromyalgia patients, they would respond to a normal physiologic dosage of T3. However, most euthyroid fibromyalgia patients require far more than normal physiologic dosages to overcome their thyroid hormone resistance.

Finally I decided that if some patients' fibromyalgia symptoms do indeed result from impaired conversion of T4 to T3, it is a rare phenomenon. I could no longer justify charging patients for the laboratory tests that would identify impaired conversion. As a result, I don't even bother ordering the tests any longer. This is the reason that you haven't read about impaired conversion of T4 to T3 and elevated reverse-T3 at this Web site or in more of our published articles.

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[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

Q&As

June 3, 2005
Question: Your article on breathing problems and hypothyroidism was a real eye opener for me. I started having air hunger shortly after my other hypothyroid symptoms began. I had never had air hunger before. It is severe enough that I can't run anymore and it's a strain to walk fast. My endocrinologist told me that I developed asthma for some reason unrelated to my hypothyroidism. He said I should see a pulmonary specialist.

In your article on breathing problems, you wrote about a study in which T3 effectively relieved the asthma symptoms of children. After some kids started using T3, they were able to stop their asthma medications.

After I read this in your article, I took a copy to the endocrinologist. I asked him to let me try T3 to see if it would relieve the air hunger. He glanced at the article and then threw it back across his desk to me. He spouted out that breathing problems have nothing to do with hypothyroidism. He also said that if hypothyroidism had caused my air hunger, the levothyroxine (T4) he'd prescribed would've relieved it.

I pushed your article back across his desk and pointed to the list of studies you quoted in the article. "These are scientific studies," I said. "They prove that some hypothyroid patients have breathing problems, and that T3 instead of T4 may relieve the problems." He pushed the article back without looking at it and said, "You can find any nonsense you want on the Internet."

I told him that if he couldn't intelligently comment on the scientific studies that contradict what he says, then he's unscientific. He was stunned and sat speechless. I asked if he was going to read the studies you listed. His face turned so red that I got scared, but I was angry, too. I told him that I hold my doctors to a higher standard of intelligence and that he was fired. I walked out and won't return.

My husband was upset about what I'd done. He said that I missed the chance to educate the endocrinologist. I disagree. I don't believe the endocrinologist was open to learning. My husband and I have argued about this, and I'd really appreciate knowing what you think. Do you think I should have handled the situation differently?

Dr. Lowe: Your question reminds me of the wide-ranging advice people have given me on how best to handle endocrinologists such as the one you describe. Some have advised me, "Pretend that their authority humbles you, and then subtly lure them to the truth so they think they discovered it." Others have advised, "Hit 'em hard right between the eyes with the scientific truth."

As a reformer, I generally take a polite but firm stance based on plausible scientific evidence. My goal of reforming some of the practices of endocrinologists, however, is long range. So, I often have the luxury of adapting my approach to varying circumstances.

But you don't have that time-permitting luxury. Your breathing problem is of *immediate* concern, and the disorder the endocrinologist is treating you for is possibly the cause of the problem. In view of this, it was entirely proper that you insisted he intelligently discuss the problem with you. And it was proper that you fired him for refusing to do so.

You also gave him a list of studies that verify that hypothyroidism is often the cause of breathing problems. The studies aren't "nonsense" from the Internet, as he implied; they are reports by reputable researchers published in credible scientific journals. Therefore, he was obliged to sensibly discuss the issue with you. Some case law, in fact, bears directly on this subject: if a doctor is going to give an opinion on a medical topic, he has a professional responsibility to be aware of the scientific status of that topic. Apparently, the endocrinologist failed in that responsibility.

Some endocrinologists are caring, courteous, rational individuals. The one you were dealing with—at least in the interaction you described—wasn't. Instead, he was ignorant of the issue at hand, dogmatic, and close-minded. With due respects to your husband's opinion, trying to re-educate a doctor of that ilk is usually a waste of time.

Philosopher Bertrand Russell wrote, "So long as men are not trained to withhold judgment in the absence of evidence, they will be led astray by cocksure prophets, and it is likely that their leaders will be either ignorant fanatics or dishonest charlatans."[1] Your endocrinologist apparently fails to withhold judgment in the absence of evidence. And, as Russell implied, his beliefs are likely to be shaped by leaders who are no more intellectually responsible than he. Your challenging and firing him, then, seems to me a prudent act of self-preservation.

I believe you employed what is the single best approach for patients to deal with an arrogant, dogmatic, and authoritarian doctor in any specialty. That approach is to *demand* that the doctor account rationally for scientific evidence that contradicts his beliefs; and if he doesn't comply, summarily dismiss him as unscientific and thereby an unworthy member of one's health care team. In short, you handled the situation in exemplary fashion, and I believe that other patients who follow your example will benefit immensely.

Continued from bottom of left page . . .

May 24, 2001
Question: I am a family physician and am interested in your work. My bother-in-law is an endocrinologist who is also a medical researcher. After looking at your published reports, he dismissed your claims, saying that your studies didn't involve enough patients. Not being a researcher, I'm not able to disagree with him. I am wondering what you have to say about his criticism?

Dr. Lowe: In clinical research, there is no universal number of patients researchers must include for study results to be credible. In some studies, many patients are needed; in others, few are required.

For each individual study, researchers must carefully calculate (as we've always done) the number of patients required. The purpose is statistical; we must know how many patients are needed so that statistical tests will show differences (if there are any) between the results of the treatment and placebo groups. If the effect of the tested treatment is weak, researchers must include more patients for statistical tests to detect a difference. The weaker the therapeutic effect, the larger the number of patients needed. If the therapeutic effect is strong, however, fewer patients are required. Some treatments are so powerful that only a single patient (used in a special study design) is needed for statistics to detect the therapeutic effect.

It is meaningless, then, to praise or denounce a study merely because of the number of patients included. To do so is to ignore the importance of several factors that interact to necessitate more or fewer patients in the study.

Even with small numbers of patients in some of our studies, statistical tests showed that the effects of the metabolic treatment were *extremely powerful*. Using more patients in the studies would have only confirmed the powerful effects. Our research funds have been meager. Expecting that the therapeutic effects of the treatment would be strong, we used a high-quality study design that would show the effects of the treatment with the smallest possible numbers of patients. As a medical researcher, your brother-in-law should appreciate the prudence of our frugality.

Even more important, your brother-in-law should appreciate another point, as any well-trained medical researcher should. Statistical tests of our study results showed something remarkable: on some measures of patient status, the probability that the differences between the treatment and placebo groups were due to chance was one in 10,000! To put this number in perspective, the differences between the groups would've been considered statistically significant if the tests had shown that the probability was only five in 100. The significance levels reached with the small number of patients show that the therapeutic effects of the treatment were *extraordinarily powerful*. Hence, the small number of patients is *not* a weakness of the studies—it is in fact a *strength*! Only one thing is more noteworthy to me than the exceptional statistical significance levels reached in these studies—the fact that experienced medical researchers and journal editors failed to understand or acknowledge what these results mean.

I would ask your brother-in-law several questions. Why it is acceptable for NASA scientists to send one man, John Glenn, into space to study the effects of space flight on the elderly? Why is it acceptable for drug companies to use single patients in studies of the dose-response curves of drugs? Why is it acceptable that a powerful technology called "behavior modification" was developed largely through studies involving single patients or few patients? And, in view of these other acceptable uses of single or small numbers of patients, why is it *not* acceptable that in some of our studies, we used the same approach?

The answer is that our use of the same approach is perfectly acceptable *scientifically*. *Politically* and *psychologically*, though, it isn't. Over the years, I've learned that most of our detractors—especially endocrinologists—don't respond with forethought to our studies and treatment approach. Instead, they react emotionally, reflexly declaring that we *must* be wrong. After all, our views differ from what their authority figures taught them. The detractors don't bother to objectively assess the evidence for our views; rather, they quickly go to work trying to justify their reflex denouncements of our views. While they're at it, they look about for *any* excuse to say we're wrong. Lacking good excuses, they swiftly stoop to using flimsy ones. Among them is the charge that we used too few patients in some of our studies.

In fairness, I can't say with certainty that your brother-in-law's criticism of our studies was emotionally or politically driven. Maybe he just isn't familiar with what dictates the number of patients required in clinical trials. This is a matter, however, that is crucial for medical researchers to understand, and I'll be happy to discuss it with him. Most likely, he has books in his own library on statistics and research methods that furnish better explanations than I can give him. After he's had time to read the explanations, I trust that he'll retract his initial criticism of our studies. As a devout critical rationalist, I'll sincerely welcome any *thoughtful* criticisms he has of the studies.

Tammy@drlowe.com

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Reference

[1] Russell, B.: *Unpopular Essays*. New York, Simon and Schuster, 1950, ,p. 27.

November 4, 2003

Question: I am a first year medical student on the East Coast. I'm interested in participating in fibromyalgia research. Can you direct me to any research teams doing work in this area?

Dr. Lowe: I appreciate your interest in fibromyalgia research. I regret to say, however, that I'm not aware of any research teams in your area that I could enthusiastically refer you to.

Our research team, on the other hand, is about to begin metabolic studies of fibromyalgia patients compared to healthy controls. We'll be using indirect calorimetry (for measuring oxygen intake and calculating the metabolic rate) and many other measures, such as body composition. We'll then use regression statistics to learn what metabolism-influencing factors account for differences we find between the patients and control subjects. If you lived in the Boulder/Denver area, we'd welcome your direct help in conducting the actual studies, perhaps in taking measurements of patients and control subjects. But since you live on the East Coast, taking part in this way may be impossible for you.

There are other ways you might take part, however, that could be educationally enriching. I'll mention two ways you might consider.

One is helping us collect copies of the journal papers we must obtain while planning and designing studies. Our research coordinator, Jane Jones, RN, and I have already collected many papers for the first of our upcoming metabolic studies, but no end ever comes to this essential task. For a student, helping in this way isn't a mere menial task. Most veteran researchers find themselves doing some—occasionally all—of this leg work. But for a student, performing it can be invaluable in developing the habit of scholarship; until all journals and books are available electronically, the leg work of library research will remain essential to acquiring a thorough knowledge of the subject under study. Acquiring this knowledge is an indispensable step in the scholarship that underlies good scientific work. Because of this, the leg work and a willingness to do it are also essential parts of scholarship.

The other way you might help is to scrutinize the content of the papers you collect, giving extreme and critical attention to every detail that may be related to our upcoming studies. By studying the papers' content, you would expand your own knowledge. At the same time, as a distance member of the research team, you could contribute to our knowledge base; the more minds we have on the team cogitating on and culling information related to our studies, the better the outcomes of our studies are likely to be. I appreciate, of course, that the demands of your medical school studies could make participation in this way an extreme challenge for you.

I hope my comments are helpful, and I look forward to hearing from you.

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Skin

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

Q&As

November 15, 2004

Question: I have been on Synthroid since 1997. The whole time, I've had extremely itchy blisters, mostly on my lower legs. I can't stand the itching, so I pop the blisters. This leaves an open sore, and twice, I've been hospitalized due to bad skin infections. Are these eruptions part of my hypothyroidism symptoms?

Dr. Lowe: I am sorry you've been troubled by the blisters on your legs. Blisters aren't a common sign of hypothyroidism. (We list the most common signs of hypothyroidism on drlowe.com.) Nonetheless, I know of two reports in which researchers described blisters as a sign of hypothyroidism.

Researchers reported the case of a 73-year-old-Japanese woman who was hypothyroid but not taking thyroid hormone.[1] Slight abrasions caused blisters to form on her fingertips, toes, and the insteps of her feet. After she began taking thyroid hormone, the abrasion-induced blisters markedly decreased. The researchers wrote that the patient's blisters were related to her low thyroid hormone level.

Other researchers reported the case of a 70-year-old man whose hypothyroidism was untreated. He had blisters on the outsides of his legs.[2] The researchers described the blisters as "pretibial epidermolysis bullosa." The term "pretibial" refers to the skin over and beside the tibia. The tibia is the bone in the front of the leg that extends from the knee to the ankle. The term "epidermolysis bullosa" simply means that the skin beside the tibia in the man responded to slight mechanical trauma by forming large blisters and erosions.

After the man began taking thyroid hormone, the number of blisters decreased; finally, they disappeared altogether. At a followup exam 12 months later, the man reported that no more blisters had formed.

The researchers conjectured that the blisters had formed because the involved skin was weak, and it was easily irritated by mild friction. They wrote that the lack of recurrences of the blisters meant that they were a feature of the man's hypothyroidism. They concluded, "Our case confirms the reality of hypothyroidism pretibial epidermolysis bullosa," and they advised doctors to test patients with skin blisters for hypothyroidism. They described another case report similar to theirs, but I haven't been able to locate it.

It is possible, then, that the blisters and eruptions on your legs are a sign of your hypothyroidism. If so, Synthroid appears to be an ineffective treatment for you, as it is for many other patients. Switching from T4-replacement with Synthroid to a T4/T3 product—with your dosage adjusted by your clinical response and not your TSH level—may permanently eliminate your blisters. I certainly hope so.

References

[1] Mochizuki, T., Tanaka, S., and Watanabe, S.: A case of hypothyroidism with bulla formation. *Dermatologica*, 1984;169(3):146-149.

[2] Le Brun, V., Boulinguez, S., Bouyssou-Gauthier, M.L., et al.: Pretibial epidermolysis bullosa and hypothyroidism. *Ann Dermatol Venereol.*, 2000, 127(2):184-187.

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Caffeine

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

Latest Updates to drlowe.com

Q&As

Antibodies and Pregnancy

May 24, 2003
Question: I'm about to start taking Isocort for adrenal support. I ordered the product from an online company. The woman who took my order said I'm not supposed to use caffeine while taking Isocort. She said to get off caffeine before starting the Isocort and to say off it. In *The Metabolic Treatment of Fibromyalgia*, you tell us that using caffeine is OK. (Thanks for including a whole chapter on the subject.) But I've now gotten used to it again, and if I'm not supposed to take it while using Isocort, I'll have to wean off it before starting the Isocort. Please let me know whether the woman is right so that I can proceed the right way.

Dr. Lowe: What the woman told you is wrong. Unless you have a special problem with caffeine, I know of no reason why you shouldn't use it while you take Isocort.

The online company you bought the Isocort from is sponsored by a group of alternative doctors. The woman who took your order was probably parroting a false belief of those doctors. Many alternative doctors hold two false and scientifically indefensible beliefs about caffeine: that it "burns out the adrenal glands" and "eats the fatty lining off nerves." Ask the doctors for scientific evidence for this putative damage and you'll learn they have none. In contrast, ample scientific evidence contradicts the beliefs.

The alternative doctors' intention is good. Their false belief that caffeine causes harm derives from a principle they subscribe to—that in general, our health is served best by avoiding or minifying our intake of chemicals foreign to the body. For most people, though, this general principle doesn't apply to caffeine. The reason is simple: Caffeine safely and effectively counteracts some of the metabolism-slowing effects of life in modern civilization. By counteracting these effects with caffeine, most people can fine tune their metabolism so that it better meets their individual needs. In this and many other respects, using caffeine is salutary, and for some people, failing to use it can be just the opposite—injurious to their health.

For the anti-caffeine fanatics among our readers, however, I quickly add: We know as well as you do that some people overdo caffeine. But the overindulgence of a few is no reason for most people to abstain from caffeine and forfeit its potential benefits.

The belief of some alternative doctors that patients should give up caffeine when using Isocort is bad advice from good guys. We've searched but never found a shred of evidence that caffeine "burns out the adrenal glands" or "eats the fatty lining off nerves." Unless you have a specific problem with caffeine, then, you're likely to be perfectly safe using moderate amounts with your Isocort. Best of luck with your metabolic rehab, including your temperate use of caffeine.

March 23, 2003
Criticism: I don't claim to have read everything you've ever written on caffeine use as it pertains to human health, but I get the impression from your statement of 1/13/03 that you assume caffeine and its various sources to be interchangeable. If in fact you are guilty of this assumption, you would hardly be alone. The medical literature is full of studies which employ coffee as a treatment variable but report its effect (if any) as that of caffeine. This is nuts.

Coffee contains over 300 organic compounds, many of which are known to be pharmacologically active or irritating. Tea must be similarly complex. That's why I hope you'll urge your readers to distinguish caffeine tablets from coffee, tea, etc.

I, for example, can take Vivarin tablets (or half tablets) with no ill effects. But a cup of coffee delivering an equivalent amount of caffeine will upset my stomach something awful.

Dr. Lowe: You're correct about the chemical complexity of coffee and tea. You're also correct about the need for clarifying for our readers that coffee and tea consumption isn't synonymous with caffeine use. I didn't realize that the content of the caffeine page of drlowe.com might leave readers confused about this important issue.

We actually recommend to patients that they use caffeine tablets, as you do. In this respect, we agree with Dr. Dean Adel's advice to his radio listeners. Using caffeine tablets is especially important for those who react to coffee or tea with gastric irritation. But it's also important for patients learning precisely how much caffeine benefits them without causing adverse effects.

Thanks for taking the time to write and point out the need for clarification.

Continued from bottom of right column . . .

October 24, 1997
Question: I read that caffeine helps with cognitive function. I am in school and having a very difficult time with exams. Is it possible I could benefit from caffeine supplements to help with cognitive abilities?

Dr. Lowe: It is highly probable that caffeine will improve your mental performance, both in studying for and in taking your exams. My clinical experience shows that this is especially likely if your cognitive abilities are impaired as part of fibromyalgia.

There are many published studies on the effects of caffeine on cognitive function. It fact, caffeine is listed as a mild brain stimulant and "cognitive enhancer." Caffeine has been reported to improve performance on tests of attention, sustained attention, semantic memory, logical reasoning, free recall, delayed recall, problem-solving, recognition tasks, mental speed-related tasks, perceptual sensitivity in visual search, reading speed, and perception of problems. Tolerance to the performance-enhancing effects of caffeine doesn't appear to develop. Caffeine has also been found to improve mood and relieve depression. Even small amounts induce users to feel more "clearheaded," happier, calmer, and less tense. In addition, caffeine consumption is correlated with a lower suicide rate.

There are other potential benefits from caffeine use, especially for fibromyalgia patients. Caffeine increases mitochondrial oxygen consumption, raises the metabolic rate, produces physiological arousal and wakefulness, increases energy level, increases internal and skin temperatures, and decreases pain (caffeine is part of many analgesic formulations because it augments the pain-killing effect of other medications).

I have at least three qualifications, however. First, determine whether you have any adverse effects from caffeine. Some people do, although in general, caffeine consumption is safe. Most "harmful" effects involve improper use. For example, some people simply consume too much and make themselves anxious or nervous. Others consume caffeine before they try to sleep and have insomnia. Reasonable precautions should obviously be exercised.

Second, for caffeine to be of benefit, you must find what for you is an effective and *non-overstimulating* dosage. This means finding the minimal amount that provides the level of cognitive function you desire, and at the same time, a dosage that doesn't make you anxious, restless, or irritable. Some people induce these symptoms in themselves by taking higher and higher doses of caffeine to further increase their energy level and improve their mood and cognitive function. But these symptoms from caffeine overstimulation can actually impede cognitive performance. The tendency of some people to impair their cognitive function with these symptoms has probably contributed to the anti-caffeine posture of many wellness advocates and holistic physicians. Typical is a statement by Dr. Ward Dean and John Morgenthaler in their 1991 book on improving mental abilities (*Smart Drugs & Nutrients: How to Improve Your Memory and Increase Your Intelligence Using the Latest Discoveries in Neuroscience*, Santa Cruz, B&J Publications, page 34): "The research we've seen suggests that coffee may have some *intelligence-lowering effects*. Unless you are truly addicted and require coffee for functioning, we recommend that coffee be avoided during intellectually-demanding situations." It's simply not true, of course, that research suggests caffeine has intelligence-lowering effects. And contrary to their view, it would be wise (based on the scientific evidence) for most people to use some caffeine before intellectually demanding tasks—that is, as long as the user consumes enough but not too much caffeine!

The third qualification concerns your own attitude toward your consumption of caffeine. Today, an anti-caffeine prejudice predominates among health care professionals and writers of self-help literature. By "prejudice" I mean that these people have concluded that caffeine is harmful without logically evaluating the available evidence. If you accept their unscientific conclusion, and while consuming caffeine, hold fearful thoughts of it harming you, you may eventually be harmed psychophysiologically by your own thoughts rather than by the caffeine (the equivalent of a disease-inducing hypnotic suggestion).

With these qualifications in mind, I would advise you to use caffeine (assuming you have no specific adverse effects from it) judiciously—that is, ignore the unscientific warnings against caffeine use, find the dosage that for you is enough but not too much, and consume it shamelessly!

More About Caffeine

Best wishes for your healthful use of caffeine.

More on Caffeine: For Most People, Moderate Caffeine Use Does Not Increase Pain

December 31, 2002
Criticism: I've just read the section on caffeine on your fibromyalgia website and can't quite believe what I've just seen. One of the most widely understood—and proven—aspects of treating this syndrome is the vital need to eliminate caffeine. In fact, eliminating caffeine is quite adequately proven to be a vital element of any healthy diet. The pro-caffeine comments on your website call the credibility of all other information put forth by your organization into serious question. As health "professionals" you should be embarrased (sic) and ashamed, if you can come down from your own caffeine highs long enough to notice. I'm absolutely appalled!

Dr. Lowe:I often think life would be easier for me if I'd submit to social pressures (exemplified by your e-mail) and climb onto the heavily-populated bandwagon of false assumptions. I can't do that, though; if I did, I'd give myself too rough a time for violating my commitment to scientific truth. Hence, I'll just have to stick with expressing beliefs I deem scientifically true and risk the occasional critic denouncing our entire website because he disagrees with one section of it.

I've debated the pros and cons of caffeine use with some physicians, such as the Internet's David Nye, M.D. Seldom have they backed up their points of view with scientific evidence. Rather, they typically argue, "The whole medical profession disagrees with you." Of course, the whole profession *doesn't* disagree with me. But even if it did, its consensus would have no bearing whatever on the truth or falsity of the question at hand: Is caffeine good or bad for our health? Only evidence—not consensus!—can show us whether this or any proposition is true or false.

My challenge to you is to present your evidence that eliminating caffeine is "vital" to patients recovering from fibromyalgia, or "vital" to health in general. I'll open-mindedly consider revising our stance on caffeine pending my review of your evidence. It must be hot off the presses. In the past, I've scrupulously studied the scientific literature on caffeine. In doing so, I've seen no evidence that moderate caffeine use is harmful to people in general—or to fibromyalgia patients in particular. Conversely, I've seen a steady growth of scientific evidence that prudent caffeine use can promote health in various ways. And many years of clinical experience have shown us that most fibromyalgia patients are helped and not harmed by the temperate use of caffeine. Despite this, as a critical rationalist, I stand ever ready to abandon my beliefs that evidence shows to be wrong. In the mean time, you'll have to excuse me while I get a cup of coffee and get back to work.

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Some fibromyalgia support group leaders and doctors believe that caffeine increases pain. For this reason they advise fibromyalgia patients to stop all caffeine use. These group leaders and doctors are wrong, and most patients would best reject their advice.

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Latest Updates to drlowe.com

Q&As

Metabolic Rehabilitation

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

Rehabilitation: The word "rehabilitate" comes from the Medieval Latin term for "habilitate," which means "to become fit." In modern English, rehabilitation (or rehab) is use of a systematic approach to people recovering health and good function. The approach restores, salvages, or reconditions a person to a state of good health and the ability to work, play, and engage in other normal activities of life.

When I invented the term 'metabolic rehab,' I did so because it involves the same *systematic work* needed to enable patients with cardiovascular and musculoskeletal problems to fully recover their health.

When performed properly, people who go through metabolic rehab use systematic measurements. They take the measurements at regular intervals. The outcome of the measurements lets the people know whether their current treatment regimen is improving their metabolism. If so, the newest measurements, compared with previous ones, let them know how much they've improved. If the improvement isn't enough, they may alter their treatment regimen in a way calculated to provide more improvement.

For most people who go all the way through metabolic rehab, the systematic process gradually enables them to live free from symptoms and other health problems that afflicted them before they began rehab to improve or optimized their metabolism.

September 4, 2007
Question: I don't understand the difference between "therapy" and "rehabilitation." Do you mind explaining what you mean by rehabilitation and especially "metabolic rehabilitation"?

Dr. Lowe: You can learn some about metabolic rehab by reading the Q&As on this page. If you're interested in the history of metabolic rehab and why I named the approach "metabolic rehab," I encourage you to read a short letter of protest I wrote. My protest was about Dr. Gina Honeyman falsely claiming that she named this clinical approach, after I taught it to her.

I regret that I had to show that Dr. Honeyman's claims was false. My attorney told me, however, that if I didn't publicly protest her false claim, I'd forfeit certain privileges involving intellectual rights. At any rate, I wrote an excoriation of Dr. Honeyman's absurdly false claim. In it, I explained a good bit about how I, with the agreement of my colleagues at the time (*long before I ever met Dr. Honeyman!*) selected the term metabolic rehab for my clinical method.

To my knowledge, Dr. Honeyman has never withdrawn her false claim, nor has she publicly apologized for misleading clinicians, patients, and others about the true origin of the term metabolic rehabilitation.

June 14, 2002
Question: I've found your website very helpful, but I'm not clear on one point. You have a lot of information on fibromyalgia on the website, but is metabolic rehab useful for patients with other diagnoses, such as hypothyroidism?

Dr. Lowe: Fibromyalgia is little more than a pattern of symptoms (widespread pain and tenderness) of some patients who have either hypothyroidism or thyroid hormone resistance. Most patients' fibromyalgia symptoms, however, are compounded and complicated by other factors that slow their metabolism. The most common of these other factors are low physical fitness, poor diet, multiple nutritional deficiencies, and the use of one or more metabolism-impairing medications.

Other patients'—those who don't have the fibromyalgia symptom pattern—have major complaints other than widespread pain and tenderness. The diagnoses doctors give the patients usually depend on the major symptom. For example, if a patient's major symptom is fatigue, she's likely to get the diagnosis of chronic fatigue syndrome. Other major symptoms that can lead to different diagnoses include depression unrelated to life events, menstrual abnormalities, high cholesterol, dry skin and mucous membranes, and the list goes on and on. Most of these patients' symptoms are compounded by the same metabolism-impeding factors that worsen fibromyalgia patients' symptoms.

What determines a patient's major symptom is the particular body tissues most sensitive to the combination of metabolism-impairing factors impinging on the patient. But despite the patient's diagnosis, metabolic rehab is appropriate. This is true because of the aims of metabolic rehab—to identify and eliminate all factors impairing the individual patient's

Continued from bottom of left column . . .

May 16, 2000
Question: I've had fibromyalgia for ten years now. My doctor has let me try several treatments that didn't work, including amitriptyline, guaifenesin, and other medications. She also recently let me try a brand of T3 called Cytomel. She knows you use large amounts, so when I didn't improve after a week with the 50 mcg she started me on, she let me increase the dose to 100 mcg. After three days, I had tremors, was anxious, and was sweating profusely. These reactions frightened me, so I stopped taking the Cytomel. My doctor thinks that your treatment is not for me. Since your protocol didn't work for me, what alternative fibromyalgia treatments do you recommend?

Dr. Lowe: Several time each week, I receive the same question from other patients. Each has the mistaken impression that she's tried our treatment protocol. But she hasn't. Let me say emphatically: Our treatment protocol is not merely taking T3. Instead, it's a comprehensive metabolic rehab process. Fine tweaking all along the therapeutic way is critical to patients improving or recovering. With each patient, we strive to paint a metabolic masterpiece, and we can't succeed by headlong splattering of T3 on the patient's canvas.

During the process of metabolic rehab, we guide the patient to improvement or recovery based on frequent feedback from her. The feedback doesn't simply involve her telling us at intervals how she's feeling. Certainly, we calculate into our therapeutic decisions the patient's subjective feelings in response to the treatment. But we also regularly use objective measures of the patient's tissue responses to treatment. We post the scores from the measures to line graphs. Then we study the graphs to learn what we must strategically do to guide the patient on toward recovery. Based on the patient's subject feelings, our observations, and the objective measures, we make revised decisions each step of the way.

So, in answer to your question, I do recommend an alternative to what you tried before—I recommend that you properly go through metabolic rehab. Your physician and you can intelligently approach your treatment by obtaining copies of my book, *The Metabolic Treatment of Fibromyalgia*. Both of you should carefully study the sections on diagnosis and treatment. Then you should start your treatment over, this time doing it according to the method that our studies have shown to be highly effective and safe. If your physician and you decide to use this informed approach, I'll be happy to answer any questions that come up during your treatment. I wish you the best of luck.

March 15, 1998
Question: Hello. My doctor and I find your T3 therapy interesting. We would like to know the name (brand name) and dosage for this therapy. He has started me on Armour thyroid 0.25 gr (15mg) tab 1 p.o. daily. Is this the right medicine, and is it the right dosage? Any information would be greatly appreciated. Thank you.

Dr. Lowe: I am pleased that you and your physician are interested in our treatment protocol. For information on the approximate proper dosage of desiccated thyroid, I suggest you read my answer on February 15, 1998 to a similar question.

I would urge you to keep in mind, however, that our protocol does *not* merely consist of taking thyroid hormone. Thyroid hormone is necessary for most patients to improve or recover (albeit unnecessary for some). In general, though, taking the hormone is not sufficient for a patient to significantly improve or overcome her fibromyalgia. Producing the necessary sustained increase in your metabolism—and especially fine-tuning that increase—involves considerably more. The indispensable ingredients include a wholesome diet and nutritional supplementation. Also, you'll have to exercise to tolerance. Many patients, however, are hardly able to exercise before beginning thyroid hormone therapy and nutritional supplementation. After beginning, they find that their capacity for exercise increases. (Of course, to detect increased capacity, you must be doing some amount of baseline activity to start with. This will give you a gauge by which to compare increases in capacity as the thyroid hormone and nutrients help to encourage those increases.)

By baseline activity, I do not mean activity that is so vigorous as to exacerbate your fibromyalgia symptoms. The intensity of your baseline activities should be below the level that would worsen your symptoms. As you find that your capacity for exercise is increasing, it is mandatory that you take advantage of that increase. The way to do that is to slowly increase your exercise intensity and frequency as your tolerance increases. And remember that throughout this process, you should be careful not to overextend yourself.

Once your symptoms have subsided, you should be able to increase metabolism, thereby enabling him or her to fully recover metabolic health. So, we treat not only patients with the fibromyalgia pattern of symptoms, but also those with a wide range of other major symptoms.

Continued at top of right column . . .

If your doctor won't order the lab tests you want, order the tests yourself. Order *any* lab test you want at discounted fees through our arrangement with Direct Labs. Fees for thyroid tests are markedly low. The low fees apply to the TSH, T3, T4, and thyroid peroxidase and thyroglobulin antibodies. Just click below and read the easy-to-follow instructions.

drlowe Metabolic Health .com

www.directlabs.com/drlowe

Tammy@drlowe.com

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the intensity and/or amount of your exercise more easily. And in doing so, you should suffer nothing more than perhaps some temporary, post-exercise soreness—soreness that would be considered normal for anyone who is increasing her exercise intensity. (You'll find additional information on our full treatment protocol in the section title "Is Treatment Available?")

When patients and their clinicians use our protocol properly, many of the patients markedly improve or completely recover from their fibromyalgia symptoms. I wish you the best in becoming one of these individuals. (Read a more detailed description of our metabolic rehabilitation and our description of what is necessary for a successful treatment outcome.)

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Q&As
Dietary or Over-the-Counter Desiccated Thyroid

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

April 14, 2011
Question: I'd like to stockpile some Thyro-Gold and some other thyroid products. How long are these products good when they are stored?

Dr. Lowe: Our biochemist tells us that from the time the thyroid glands are collected from animals, the thyroid powder produced from them is good for about three (3) years. It's at the end of three years that a follow up certificate of analysis is required for a particular numbered batch of thyroid raw material.

Various conditions, of course, may decrease the potency of any thyroid product before three years have elapsed. In my criticisms of the British Thyroid Association's false claims and misleading statements about desiccated thyroid (section "Instability of T4 Products," p.3), I quoted Eric P. Duffy, PhD, Director, Division of the Post-Marketing Evaluation Office of New Drug Quality Assessment at the FDA.

In 2006, Dr. Duffy wrote of T4 (levothyroxine sodium) products: "Levothyroxine sodium (T4) is labile to [prone to reduced potency] by the following: *Heat, moisture, oxidative conditions, chemical reactions*. These conditions typically occur during levothyroxine formulation, tableting, packaging,
and storage."

He also wrote, "*Many* levothyroxine drug products have exhibited [a] history of suboptimal stability profile, significant loss of potency over shelf life, [and] inconsistent stability profiles within an individual manufacturer's drug product line." (Italics mine.)

Dr. Duffy was talking about products that contain only T4, such as Synthroid and Levoxyl. I don't know whether the range of other thyroid hormones in dietary desiccated thyroid are as vulnerable to deterioration as is T4. But the shelf life may be maximized if you store Thyro-Gold and other thyroid products so as to avoid the degrading conditions Dr. Duffy listed that can cause instability of the potency of T4 products.

October 12, 2009
Question: Why do endocrinologists like Dr. Richard Guttler bash desiccated thyroid and push T4? I don't understand the differences in opinion between alternative doctors like you and regular endocrinologists like Guttler.

Dr. Lowe: In her September 2009 newsletter titled *Stick Out Our Necks*, thyroid patient advocate Mary Shomon announced an article I wrote for *Thyroid Science* on Guttler's idiotic views on desiccated thyroid. I'll quote parts of what Mary wrote as an introduction to my article. Then I think it would serve you well to read my article itself to see how truly nutty are Guttler's statements about desiccated thyroid.

Mary titled her article, "Dr. John Lowe Debunks Dr. Richard Guttler's Controversial Claims about Natural Desiccated Thyroid." She then opened with: "Researcher Dr. John Lowe, editor of the journal Thyroid Science, has made it his mission to get to the truth of issues surrounding thyroid diagnosis and treatment."

Mary then eloquently gets directly to the point: "Dr. Lowe's latest analysis focuses on the science behind natural desiccated thyroid (NDT) drugs, and the criticisms of natural thyroid made by a controversial and frequently volatile California endocrinologist, Richard B. Guttler, who for decades has been an extremely vocal and volatile opponent of natural thyroid drugs, synthetic T3 medications, and patient rights to choices in thyroid hormone replacement medication."

"According to Dr. Lowe," Mary wrote, "In this paper, I provide more evidence that [Dr. Guttler's] allegation against NDT is false. I believe it is crucial to the health and well-being of many hypothyroid patients that Guttler open-mindedly acknowledge the falsity of his claim that NDT does not provide benefits. Some clinicians may accept without question his false claim and deny patients NDT as a potentially effective alternative when they fail to benefit from T4 replacement." Maybe he believes the old Nazi line that, "Repeat a falsehood loud enough and long enough and everyone will eventually believe it's true."

Mary then wrote in conclusion, "Find out more about Dr. Lowe's analysis." The link is below, and I trust that you'll see how wrongheaded Guttler is by reading the article. She provides a link to it on her webpage below, and she provides links to other relevant Guttler issues.

http://thyroid.about.com/b/2009/09/28/john-lowe-richard-guttler-natural-thyroid.htm

September 26, 2009

Q&As
Armour Thyroid, Erfa Thyroid

—Continued from lower right-hand column:

November 25, 2003
Question: For many years, I was on T4 for my hypothyroidism. It kept my TSH level at about 2.0, which my doctors consider normal. Unfortunately, I had hypothyroid symptoms the whole time. Based on one of your newsletters, I went out on the Internet and purchased an over-the-counter [OTC] natural desiccated thyroid product. The company I bought it from advertises that you recommend their product. The product claims to have 130 mg of dissected thyroid hormone in each capsule. After four weeks on the product, my TSH level went up from 2.0 to 96! My conclusion is that there are no hormones in this product!

When my doctor saw how high my TSH went up, he put me on 60 mg. of Armour Thyroid. He prescribed Armour because I refused to take another T4 product. After four weeks, my TSH went down from 96 to 2.29! I'm doing very well on the Armour. In fact, I haven't felt this well in many years, even though I was taking T4 all that time!

I don't know whether the OTC product I took really contains 130 mg of desiccated thyroid. But no one should have to experience what happened to me! I really want to hear what you think about this. What, if anything, do you intend to do about it?

Dr. Lowe: You're not the first person who has written to us about this issue, and it certainly deserves comment.

Your increased TSH level while you were using the OTC product indicates one of two things: (1) you were taking too few of the capsules, or (2) the capsules had little or no thyroid hormone in them.

You didn't tell me how many of the capsules you were taking each day; because of that, I don't know whether you were taking too little to keep your TSH down.

Assuming for the moment that you were taking enough, the capsules may have contained too little thyroid hormone. The thyroid hormone in *all* brands—both prescription and OTC—is highly susceptible to degrading. Because of this, all thyroid hormone products are subject to losing some or all of their potency. When they do, we say the products are "subpotent." Subpotent batches of Synthroid and Levoxyl have often been recalled by the FDA. And over the years, an occasional patient of ours has found that the Armour, Cytomel, Cynomel, or other brand of thyroid hormone she was taking was subpotent.

In our experience, only a small percentage of prescription products are subpotent, and a higher percentage of OTC products are subpotent. Unfortunately, we don't know exactly what percentage of OTC products are subpotent.

We find that prescription thyroid hormone products generally—but certainly not always—provide more predictable clinical results. Still, though, we've found that most patients who use OTC thyroid hormone have had satisfactory results. Many patients we know have fully relieved their hypothyroid symptoms with OTC products after doctor-regulated therapy with prescription products failed to do so.

July 8, 2003
Question: I read your new book *Your Guide to Metabolic Health*, and I'm truly impressed. I learned many things to try to get into a healthy routine. But I bought the book for my mother. She's hypothyroid and has fibromyalgia symptoms. I was so glad that in the book, you support every issue I've brought up to Mom, especially that she should be using a thyroid hormone product that contains both T4 and T3. She's taken Synthroid for many years and it hasn't helped her. I explained that Synthroid has only T4 in it, and now she's willing to ask her family doctor for a product that contains T4 and T3.

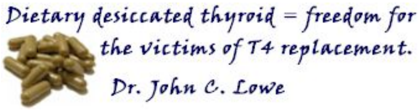
Family doctors are oblivious to how to correctly treat hypothyroidism, but maybe hers will listen if she tells him what to prescribe instead of Synthroid. Can you give me the name of some prescription products that contain T4 and T3? Knowing what to ask for is a step in the right direction. Hopefully he'll cooperate, and then my prayers may be answered and she'll finally get well.

Dr. Lowe: Thanks for your kind estimate of *Your Guide to Metabolic Health*. It sounds like you plan to improve your own metabolic health with the methods we describe in the book, and perhaps your mother will, too.

Question: I'm confused. I read a study of yours at *Thyroid Science* and you say in it that Thyro-Gold, which doesn't require a prescription, works as well as the T3 thyroid hormone called Cynomel. But I keep reading statements on web sites that the over-the-counter thyroid products don't work well. At one website I read this morning, somebody asked about an over-the-counter thyroid product called Nutri-Meds. She wrote: "I was wondering if anyone takes Nutri-Meds thyroid medication. Are you satisfied with this product? Just if anyone has personal experience to share cause Armour is hard to get without a prescription."

Here's the answer somebody gave her: "Nutri-Meds is a non-prescription brand of natural thyroid. Patients report that over-the-counter thyroid products, including Nutri-meds[sic], are *FAR* weaker than all the above [referring to Armour]. Yes, they may be good in a pinch for help, but not for long term support."

In your study, you found that Thyro-Gold works as well as Cynomel. If that's true, then why do these people say that the over-the-counter thyroid products don't work all that well?


Dietary desiccated thyroid = freedom for the victims of T4 replacement.
Dr. John C. Lowe

Dr. Lowe: The person who gave the answer is right only in one sense: If you compare the effects of a dietary (nonprescription) desiccated thyroid to prescription desiccated thyroid, *and you use the exact same weight of each*, you'll see that the dietary product is weaker. But if you use *enough* of the dietary product, you'll induce the same measurable physiological effects as you can with any other type of thyroid product.

No offense intended, but the person's statement that such products are "good in a pinch for help, but not for long term support" is simply wrong. I know this for two reasons. First, over the years in my clinical practice, I consulted with *scores* of patients who recovered their health—and maintained it for years—by using a variety of dietary desiccated thyroid products.

However, for a more solid reason, I know that some of the products, such as Thyro-Gold, work as well as any other thyroid hormone products, over-the-counter or otherwise. I know this because for the past three years, I've conducted (and am still conducting) clinical trials with dietary desiccated thyroid. The main product I've tested, as you obviously know, is Thyro-Gold. But Thyro-Gold isn't the only preparation I've tested.

As a result of this year of extensive research, I've done hundreds of metabolic measurements and other objective tests. I've statistically analyzed the massive data, and the results show unequivocally that *when used properly*, these products do indeed usually work. However, those three italicized words—*when used properly*—are crucially important to getting satisfactory results from using the products.

No matter which of the products a person uses, he or she must use it properly. I've provided a good deal of information on proper use at ThyroidScience.US. (You can learn a lot at that site from free chapter downloads, and from three particular Q&As at the site. One Q&A is on how to find the dose that's right for you, keeping track of how your treatment is progressing, and how to avoid overstimulation.)

I've read some distinctly negative criticisms of dietary desiccated thyroid by some highly-vocal naysayers on the Internet. From my communications with a few of them, I got the distinct impression that they negatively judge the products for one main reason: They used one or more of the products expecting them to work like magic bullets. Their attitude was, "Swallow the capsules for a week or so, and if they're any good, that's *all* I should have to do to get well.

These people's attempts to get well failed because they failed to learn a simple fact—precious few people get well simply by taking thyroid hormone, whether it's over-the-counter or prescription thyroid hormone.

Most anyone who's going to recover his or her health with thyroid hormone must—absolutely *must*!—at minimum engage in lifestyle practices that are synergistic to thyroid hormone. That means adopting a wholesome diet, taking a wide array of nutritional supplements, exercising to tolerance, and declining to use a number of Big Pharma's drugs that impede metabolism.

I worked with countless patients when I was in clinical practice, and since then, untold other consulting clients, who didn't benefit much from dietary desiccated thyroid until they adopted such health-inducing and health-sustaining lifestyle practices.

In short, then, I respectfully disagree with the people at various websites who denigrate dietary desiccated thyroid products. When used properly, and within the context of a health-sustaining lifestyle, most such products effectively *help* maintain normal metabolism and optimal health. I italicized the word "help" because most people must have those other factors working along with thyroid hormone on their behalf.

November 8, 2004
Question: I've had hypothyroid symptoms for years, but they've been diagnosed as fibromyalgia and chronic fatigue. I don't have health insurance, I have very little money, and can't pay your fees or those of other consulting doctors either. I would like to know how to get desiccated thyroid without a prescription. Please let me know. Thank You.

Dr. Lowe: I sincerely regret that you've suffered so long from hypothyroid symptoms. I am also sorry that you're in a compromised financial circumstance; I understand and sympathize.

Over-the-counter (OTC) desiccated thyroid is available through many websites on the Internet. All you have to do is type into any search engine the words "desiccated thyroid." Many sites that sell products will

Doctors have a choice of prescribing any of several brands of thyroid hormone that contain T4 and T3. Armour Thyroid is the most commonly prescribed brand. (Erfa Thyroid from Canada is competing well with Armour now) Armour is desiccated (dried) thyroid taken from pigs. Thyrolar is a synthetic brand that contains the same ratio of T4 to T3 as Armour.

Many of our hypothyroid patients use Armour. Most of them fully recover from their hypothyroid symptoms when they reach a high enough daily dose. It's noteworthy that the patients recover with Armour after having failed to improve enough—*if at all!*—with the use of Synthroid, Levoxyl, or other brands that contain only T4. A small percentage of patients do well with brands that contain only T4. But many years of clinical experience have compelled us to a firm conclusion: Brands containing T4 alone provide most hypothyroid patients with distinctly inferior treatment results. Because of this, none of our patients use such brands anymore.

I hope your mother's doctor will cooperate and switch her to a more effective thyroid hormone product than Synthroid. If he does, you're likely to see her undergo a rapid and full recovery—assuming, of course, that she uses the other metabolism-regulating therapies and lifestyle practices I describe in *Your Guide to Metabolic Health*. Please give your mother my best wishes.

Tammy@drlowe.com

Our Educational Consulting Service

We provide educational consulting to both patients and clinicians. Phone us at 603-391-6061, or preferably, write to us at Tammy@drlowe.com. Our fax number is 303-496-6200. ***—Tammy Lowe***

February 15, 1998
Question: Four years ago I was diagnosed with fibromyalgia. I have had my thyroid level tested and my doctor tells me it comes back "normal". She has, at my request, prescribed Armour Natural Thyroid at 60 mg daily. Is this enough?

Dr. Lowe: Whether 60 mg of Armour is enough for you must be determined by you and your physician. In general, however, 60 mg is not enough for improvement or recovery from fibromyalgia. It should help to put this dosage of Armour (desiccated thyroid) into proper perspective. To do so, I'll convert your dosage of Armour into the equivalent dosage of T4 (thyroxine) required for most hypothyroid fibromyalgia patients to improve or recover.

Most hypothyroid fibromyalgia patients respond only to 200-to-400 micrograms of T4 (0.2-to-0.4 milligrams). Few patients benefit from the 100-to-200 micrograms of T4 that most clinicians unjustifiably restrict them to. Some writers state that your dosage, one grain (65 mg), of desiccated thyroid provides the equivalent of 80 micrograms of T4. [Actually, desiccated thyroid contains both T4 and T3]. For example, one grain of Johnson's desiccated thyroid contains 38 micrograms of T4 and 9 micrograms of T3. T3 is often reported to be four times more potent than T4. Thus, in terms of potency, the 9 micrograms of T3 is roughly equivalent to 36 micrograms of T4 (9 x 4=36). So it could be argued that the total potency of the thyroid hormone in one grain of Johnson's desiccated thyroid is equivalent to about 74 micrograms of T4 (38 micrograms from T4 + 36 micrograms from T3 = the potency equivalent of 74 micrograms of T4).]

From this consideration, one might assume that to benefit from Armour thyroid, a patient must take enough to equal the potency of 200-to-400 micrograms of T4. If this were true, it would be necessary to take between 2½ to 5 tablets of Armour per day. (2½ tablets would have a potency roughly equivalent to 200 micrograms of T4; 5 tablets would have a potency roughly equivalent to 400 micrograms of T4.) But this assumption would be incorrect. Most hypothyroid fibromyalgia patients improve on lower dosages of Armour than this. The likely explanation is that the potency of the T3 in the Amour is actually equivalent to more than four times the potency of T4. Some recent publications suggest that T3 may be 10 times more potent than T4.

The bottom line is this: While mathematical conversions can be fun, they don't help us determine how much Armour a patient will need to improve. A patient's effective dosage must be determined on an individual basis, with the patient and physician closely cooperating. To find that dosage, the patient's fibromyalgia status should be objectively measured repeatedly (as with the five fibromyalgia measures we use in our research studies). So should certain physical measures, such as the Achilles reflex and pulse rate. A comparison of the repeated measures as time passes will show whether the patient is benefiting from a particular dosage. If not, the physician may need to gradually increase the dosage until the repeated measures indicate improvement or recovery. In most cases, the patient's subjective assessment of his or her improvement corresponds closely with the changes in the objective measures. And it's important to remember that the patient's TSH level is of no value in determining the proper dosage.

The response to desiccated thyroid is difficult to predict simply come up.

If you're going to use an OTC desiccated thyroid product, you should first read all of this page of Q&As and my Q&A page on desiccated thyroid. You should also get a copy of my book *Speeding Up to Normal: How to Safely Get Well with Thyroid Hormone*.

The book is a by-the-numbers guide to self treatment, and it includes important educational information on using thyroid hormone *safely* and *effectively*. We wrote the book mainly for patients such you, whose limited personal finances prohibit them from paying for professional services.

I also recommend that you get a copy of Dr. Barry Durrant-Peatfield's book, *The Great Thyroid Scandal and How to Survive It*. In the book, Dr. Durrant-Peatfield gives a great deal of practical information that's important to patients guiding themselves through metabolic treatment with desiccated thyroid. The publisher's website for the book is http://www.baronsdownpublishing.com/ordercc.htm.

These books will give you more accurate and advanced information about thyroid hormone therapy than most conventional doctors have in their heads. With the information, you'll stand a far better chance of recovering than you would under those doctors' care. If you run into obstacles along the way, we'll be happy to help you through brief long-distance consulting. Many patients get themselves well through self treatment, and I sincerely hope you're soon one of them.

—Continued at top of right column

through mathematical conversions. However, many patients benefit from it after they've failed to benefit from T4 alone.

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Q: I have started taking the Hypo Support Formula because I could not get Armour. I am taking four capsules right now and the total selenium in those four caps is 400 mcg. I have not reached an adequate level of thyroid supplementation yet and I am concerned about taking too much selenium. I am very chemical sensitive and do not metabolize things at a normal rate. I am hoping the thyroid will end up helping that, but until it does, if it does, how much selenium is safe to take and is there a possibility that I can become toxic with it. Also, when will your new thyroid formula be available and will there also be the selenium in it? Thank you so much for your help and also for all the work you do to get the facts out to the public. March 31, 2010

Dr. Lowe: The question you asked about selenium is the most common question we've received from people taking HSF. Because of that, Franconia is soon sending out a special newsletter to the customers of ThyroidScience.us. The topic is exactly what so many of them are concern is about: the possibility of selenium poisoning from HSF, especially if a person is also taking RLC Labs' Thyro Multi. I hope you'll find what I've written on the topic of interest, and I'll appreciate any comments you have after reading the newsletter.

To directly answer your question, I don't think you're at risk of selenium poisoning from the 4 capsules of HSF. As I point out in the newsletter I mentioned, in an epidemiologic study in China, people developed selenosis (selenium poisoning) on average from 1270 mcg of selenium each day. You're taking far less than that amount in the HSF. Of course, one must consider the total daily intake of selenium from HSF and other sources, such as Thyro Multi.

As I point out in the newsletter, we must also consider the matter of individual sensitivity to selenium. You wrote that "I am very chemical sensitive." That being the case, you might be especially interested in the issue of individual sensitivity.

Latest updates

New Life Multi
Organic, Raw Foods
Multi Supplement
(Replaces Thyro Multi)

I'm apparently particularly sensitive. From taking 10 capsules of HSF per day, along with 3 capsules of Thyro Multi twice each day, for 3 months, I developed reversible spastic paralysis. When I suggested that to a key person at RLC Labs that the company reduce the amount of selenium in HSF, he declined. After I recently did a trial of 10 capsules of HSF, this time without taking Thyro Multi, I again developed spastic paralysis that was relieved several days after I stopped taking the HSF.

Again, I think you're highly unlikely to develop selenosis from 4 capsules of HSF. And my communications with others who take HSF suggest to me that on average, 6 capsules per day aren't likely to cause symptoms of selenosis. I encourage you, though, to calculate your total selenium intake from all sources, and to consider your individual sensitivity to the element.

To answer your last question, the new product should be available in 4-to-6 weeks. It will contain no selenium whatever. I hope this is helpful to you, and I wish you all the best.

Common Symptoms of Selenosis

Bluish skin
Breathlessness
Cough
Chest pain
Cracked nails
Dry cough
Fatigue
Fever
Fibrosis of lungs
Garlic-smelling breath
Hoarseness
Inflamed lungs
Loss of appetite
Malaise
Nail grooves
Paralysis
Rapid breathing
Scarred lungs

Shallow breathing

Shortness of breath

Sleep problems

GI upset

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AskDrLowe

Most Recent Q&As

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Hyperthyroidism & Fibromyalgia | Hypometabolism | Hypothyroidism & Fibromyalgia
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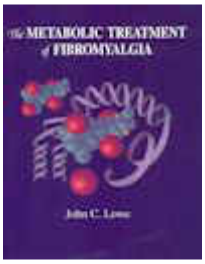

The Metabolic Treatment of Fibromyalgia
by Dr. John C. Lowe
Readers' Comments

Read about Your Guide to Metabolic Health

Medicines Commonly Prescribed for Fibromyalgia

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

April 24, 2002

Question: I read that you and your wife, Dr. Gina Honeyman-Lowe, don’t work with patients taking narcotic medications for fibromyalgia. Since many fibromyalgia patients must use narcotics for pain relief, why do you feel this way?

Dr. Lowe: First, let me clarify our position regarding patients' use of narcotic medications. We make no value judgments about patients using narcotics, and we personally have no objections to patients choosing to do so. When patients use narcotics on an occasional, as-needed basis, this doesn't interfere with them improving or recovering when they go through metabolic rehab. We've learned, however, that most patients using maintenance doses of narcotics (taking them each day at intervals through the day) fail to benefit from metabolic rehab.

We have roughly an 85% success rate with fibromyalgia patients; that is, only about 15% of patients who fully cooperate with our protocol and complete treatment fail to markedly improve or fully recover. Prominent among this 15% who fail to recover are patients using maintenance doses of narcotic medications. We've tried to learn why these patients fail to improve and found two main problems.

The first problem is that narcotics appear to sensitize some brain centers to thyroid hormone. The evidence for this is sketchy, but the little evidence we've found provides a plausible explanation for an observation of ours: Some fibromyalgia patients taking maintenance doses of narcotics develop symptoms of over-stimulation at doses of thyroid hormone too low to enable them to recover. The apparent over-stimulation makes it impossible to raise their doses of thyroid hormone to therapeutic levels. When this becomes obvious, the only practical choices for the patients are to stop their narcotics or discontinue metabolic rehab.

With *some* patients who must make one of these choices, the second problem then arises. These patients don't want to stop the narcotics. Without hesitation, they choose to forgo the chance to improve or recover with metabolic rehab rather than give up the narcotics.

When we and our cotreating doctors have pressed these patients to stop the narcotics, they come to exhibit a complex of "drug-seeking behaviors." One behavior is hostility toward us for suggesting that they've become addicted to the narcotics. Objective measures may indicate that the pain of some of them has improved, but they'll insist that they’re still in pain and must continue using the narcotics. On the other hand, some patients indicate that they’re in 100% pain even with narcotic use. Despite this, they refuse to consider that since the narcotics haven't improved their pain at all that they should cease using them—at least temporarily—to give a promising alternative approach a chance to work. We’re convinced that some of these patients want to maintain a diagnosis of fibromyalgia as a ploy to continue their narcotic use.

As a pain management specialist, I was slow to face the reality of narcotic addiction of some fibromyalgia patients. The reason is that several years ago, I agreed that doctors were too restricted in their privilege of prescribing narcotics for patients in incorrigible pain, and I favored loosening of the restrictions. But as a fibromyalgia specialist determined to get each of our patients well, I have no choice but to face the fact that narcotic addiction becomes an obstacle to some patients' recovery.

I want to emphasize an important point: We know that narcotic use is a boon to many patients who live with chronic pain from which there is no available escape, and we have no objection to such patients using narcotics. Most patients' fibromyalgic pain, however, is escapable, although narcotic addiction often becomes a roadblock to the escape.

Unfortunately, discussing this subject openly carries a distinct risk. Many patients using narcotics—including some doctors with a diagnosis of fibromyalgia who liberally prescribe narcotics for their patients—promptly join campaigns of hostility toward doctors who express concern about narcotic addiction. We have no choice, though, but to be honest with patients using narcotics who inquire about treatment with us. For us not to discuss the subject forthrightly would be unethical.

The patient using narcotics and who wants to undergo treatment with us has two options. First, she can, before starting treatment with us, enlist the cooperation of the doctor who prescribes her narcotics in helping her stop the medication. Or she can commit to stopping the narcotic (again with the cooperation of the prescribing doctor) shortly after beginning metabolic rehab. If a patient chooses to continue taking maintenance doses of a narcotic, the chance of treatment failure with us is high. Again, we make no value judgment about a patient’s choice either way, but professional ethics compel us to be honest about the issues involved. I hope this clarifies our position on fibromyalgia patients’ use of narcotic medications.

January 24, 2002

Question: Are you aware of the fibromyalgia drug called milnacipran that Cypress Bioscience is working on? If you are, what do you think of it?

Dr. Lowe: Milnacipran is a drug that acts on two neurotransmitters, serotonin and norepinephrine, involved in pain modulation. The intent of this drug as a fibromyalgia treatment is to decrease patients’ pain.

I’m certainly in favor of fibromyalgia patients, if they must, prudently using some drugs to control their symptoms—at least until they undergo effective metabolic rehab to correct their symptoms’ underlying cause. I don’t question that Cypress Bioscience is motivated by a desire to relieve the suffering of fibromyalgia patients. And I don’t doubt that the corporation believes that providing milnacipran is an expeditious way to accomplish that desire.

At the same time, projects such as Cypress Bioscience’s development of milnacipran cause me grave concern. To develop milnacipran as a fibromyalgia treatment, and to get FDA approval for the drug, involves a huge financial investment by the corporation. For me, that investment represents a troubling implication. The corporation (if it’s run competently) must recoup its investment and produce profits. For this to happen, the corporation must count on the drug working well as a stop-gap method for reducing fibromyalgia patients' pain. The corporation must also either be (1) unaware that an effective treatment that corrects the underlying causes already exists, or (2) count on an indefinite delay in patients becoming aware of that cause-correcting treatment.

My personal belief is that the project by Cypress Bioscience is exactly what we don’t need in the field of fibromyalgia: another corporation developing a patentable drug that does nothing more than reduce fibromyalgia patients’ pain. Instead, we need to focus on the underlying causes of the pain. Only by focusing on underlying causes can we truly free fibromyalgia patients from their pain and other symptoms. The approach of Cypress Bioscience (if milnacipran is effective) will only reduce patients' pain while the causes continue apace.

Merely providing drugs that diminish symptoms rather than eliminating causes has long been a strategy of medically-related corporations for providing themselves long-term financial profits. Typically in modern medical science, a corporation comes up with a drug that modestly controls the major symptom of a disorder. Then the corporation begins to successfully market the drug. At that point, market forces come to militate against researchers eliminating the cause of the disorder. The corporation usually heavily funds a group of researchers in the field, and this group conducts steadily more studies related to that particular drug. These researchers' study results are readily published in major medical journals where the corporation pays lavishly to advertise the drug. In addition, the corporation sponsors (through financial-donations) well-publicized conferences where these researchers present their study results. The minds of practicing doctors are potently influenced by the highly visible published reports and conference presentations of these corporate-sponsored researchers. The practicing doctors presume that the drug represents the cutting-edge of science in the field.

This collaborative venture of corporations, researchers, major medical journals, and conferences effectively controls the minds of practicing mainstream doctors and their patients. Through this control, the venture easily undermines the work of other researchers studying the underlying causes of the disorder—causes that may be totally unrelated to the drug. Subverted in this way, the other researchers' work at best dimly shows through a veil of obscurity; their work remains poorly funded and largely ignored. Hence, the causes of the disorder persist and patients remain ill, yet those involved in the venture reap continuing financial rewards.

These observations bring me personally to conclusions that Cypress Bioscience probably won't like. First, to develop milnacipran as a fibromyalgia treatment is an expenditure of time, energy, and money that could be *far* better spent in clarifying the underlying causes of fibromyalgia. Second, this effort by Cypress Bioscience (and similar ones by other corporations) forebodes an ominous future for fibromyalgia patients under mainstream medical care.

Q&As

Adrenal Glands

[Q&As are placed in reverse chronological order. In other words, the latest Q&As come first. Earlier ones are further down the page.]

Dr. John C. Lowe

How to lower sleep-disrupting high cortisol at night (Serophos)
August 27, 2010

Adrenal Fatigue—A Real Disorder No Matter What its Name: A Response to Dr. Peter Hibberd

July 19, 2008
Question: Thank you for our phone consultation yesterday. I have an additional question for you. From what I am reading about adrenal fatigue, my symptoms seem pretty severe. I have read in several sources that there is no harm in replacing cortisol at a physiologic dose. If the body doesn't need it, it will not cause any harm if the patient weans off it slowly. But if the body does need it, signs of benefit will show fairly rapidly.

Here is what I am wondering. My ability to work is almost non-existent. I am having to put my head down on my desk at least every 20 minutes and am really struggling just to make it through the day. I know I am supposed to do the saliva tests, but I am extremely concerned that I'll become worse while waiting for this process to take place. I am wondering if you're willing to recommend that I immediately start the Cortef prescribed last week by the doctor who referred me to you for consulting? I believe doing a trial of Cortef [hydrocortisone] could be diagnostic in its own right, and I will then use saliva testing to regulate my dosing if I show improvement.

Dr. Lowe: Regarding your suggestion that you begin to use Cortef based on your symptoms, your prescribing doctor is the clinician who must authorize you to do an empirical trial of the medication. Based on clinical experience, I don't think you're likely to harm yourself by a short empirical trial of Cortef, even if you actually don't need more cortisol or if you have an excess.

However, in that my relationship with you is educational, I must point out an observation from my clinical practice. I have had several patients, all of whom had classic cortisol deficiency symptoms, who turned out to have high rather than low cortisol levels. We learned this as soon as we received their salivary cortisol test results. These patients immediately ceased taking cortisol, and some had to use cortisol-suppressing agents to produce a normal diurnal cortisol pattern.

The brief cortisol trial did these patients no apparent harm. In principle, though, considering the outside likelihood of adverse effects, you may want to err on the side of caution. A patient who decides to try cortisol empirically before we receive her cortisol test results stands some chance, low as it might be, of inducing cushingoid symptoms, such as increased belly fat.

Other cushingoid symptoms include mental and emotional lability. I know you're suffering now, and I wouldn't want you to worsen how you feel. Waiting for your cortisol test results is tough enough, but a risk in doing an empirical trial of Cortef—if you have high rather than low cortisol—is worsening any unpleasant mental and emotional effects you're now suffering from.

When a patient adds cortisol to an already high cortisol level, she risks inducing damage to hippocampal cells in the brain. This can cause a loss of short term memory. Excess cortisol can also suppress immune function, making the patient more susceptible to infections. And as I explain in *The Metabolic Treatment of Fibromyalgia*,[1,p.487] long-term excess cortisol levels can cause a loss of bone mineral density.

Of course, I understand your sense of urgency. In view of the risks, you may be willing to take the gamble and use Cortef to see if it reduces or eliminates some of your troubling symptoms. If you decide to take the risk, however, you must have your prescribing doctor's approval, as we must respect his province in this circumstance. If he and you decide to commence with a trial, I'll be happy to help both of you decide how it affects you.

January 2, 2008
Question: I am a naturopathic doctor and have hypothyroidism and adrenal insufficiency. I've been taking medication for these conditions over the past several years. Despite experimenting with different dosages and combinations, I am yet to find the correct

—Continued from bottom of left column

December 10, 2006
Question: I am a 46-year-old woman who has been hypothyroid for twenty years. The general practitioner who diagnosed my hypothyroidism put me on Thyrolar. I did well on that for years. When I saw an endocrinologist for another problem, she took me off the Thyrolar and prescribed Synthroid. She told me that Synthroid was the standard of practice. Within three months, I had gained fifteen pounds and was severely depressed. My general practitioner prescribed an antidepressant for the depression and told me to exercise more to lose the weight. Out of frustration, I found a new general practitioner, and he prescribed Armour Thyroid. Six weeks later, my weight was down and the depression was gone.

About a month after I started the Armour, a new problem came over me. My joints became swollen and painful. My finger and wrist joints are worse, but my shoulder and hip joints also hurt. A rheumatologist who gave me a cortisone shot, and the pain was gone for about a week. When the pain came back, he told me to take ibuprofen to keep the pain down. I'm doing that, but my joints still hurt and I'm afraid of side effects of the ibuprofen. Do you think I became allergic to something in the Armour? Should I switch back to the synthetic hormone in Synthroid to see if that makes the pain go away?

Dr. Lowe: I'm sorry you have joint swelling and pain, and that you're confused about what brought it on. I think it is highly unlikely that you're allergic to anything in the Armour pills. A way to eliminate that possibility, however, is to take an antihistamine that you know is effective for you. If the antihistamine makes the swelling and pain go away, stop the antihistamine. If the swelling and pain return, start the antihistamine again. If the symptoms again subside or fully go away, you can be confident that an allergy is causing the symptoms.

As I said, though, I think that's not likely. I have two reasons for saying this. First, the rheumatologist's cortisone injection stopped the swelling and pain for a time. Cortisone is an anti-inflammatory drug, and because it stopped the swelling and pain, the cause is most likely inflammation.

My second reason for saying an allergy isn't likely the cause of the symptoms is more important. That reason is that I've had many patients who had essentially the same history as you. They had joint swelling and pain after switching to a more effective thyroid hormone therapy. (Most often, patients had switched from a T4-only product, such as Synthroid or Levoxyl, a T4/T3 product such as Armour, Thyrolar, or Erfa Thyroid, or to T3 alone.) I then diagnosed a cortisol deficiencies through salivary free cortisol testing. Next, we corrected their deficiencies with physiologic cortisol therapy, and this eliminated their joint swelling and pain.

If you're truly like those patients, what probably happened to you is this: Synthroid was not effective enough to keep your liver's metabolism at a normal rate. Because of this, your liver sluggishly cleared cortisol from your blood. For some reason, the cortex of your adrenal glands can't produce a normal amount of cortisol. But, using Synthroid and only slowly clearing cortisol out through your liver, you still had enough cortisol in your body to inhibit inflammation.

But when you switched to Armour, it sped up your liver's metabolism. As a result, your liver began clearing cortisol from your body more quickly. But your adrenal glands can't produce enough cortisol to make up for the larger amount your liver is clearing from your body. Because of this, the faster clearance has lowered your body's cortisol too far. Having too little of this anti-inflammatory hormone has led to your symptoms: joints that are swollen and painful from inflammation set off the mechanical stresses of joint movement and weight bearing.

If a cortisol deficiency has caused your joint swelling and pain, switching back to Synthroid is not the prudent course of action. Synthroid might free you from the joint swelling and pain by letting your liver again clear cortisol from your body too sluggishly. But you would most likely gain weight again and sink back into depressed. What is prudent is to stay on Armour Thyroid, which is more effective for you. Then confirm that you have a cortisol deficiency, and correct it by using physiologic cortisol therapy.

December 14, 2003
Question: I took Armour Thyroid for a month. It relieved most of my hypothyroid symptoms, but then I began to have severe joint pain. I've now been off the Armour for six weeks. My old hypothyroid symptoms have returned, but the joint pain has stopped. My endocrinologist prescribed the Armour, and he was very surprised. He's never had another patient who had this problem. I contacted Forest Pharmaceuticals, the manufacturer of Armour, and they said they had six other cases like mine. When the patients took Armour, they developed joint pain, and the pain went away when they stopped

doses. I did feel well and stable for 18 months while on a combination of 50 mcg T3 and 15 mg of hydrocortisone.

After a large stress, however, I developed hypothyroid symptoms again. I increased by T3 to 70 mcg, but all that did was keep me awake and not relieve my symptoms. My doctor tested me and said that my TSH levels showed that I was hyperthyroid. Because of this, he lowered my dosage to 30 mcg of T3 and added 25 mcg of T4. I became severely ill on this and my health declined drastically over six months. My doctor refused to change the medication because now my TSH level was back to normal.

On my own, I added two grains of Armour per day and improved very quickly. Under the care of another doctor, I'm now on 4 grains of Armour per day and 15 mg of hydrocortisone. I'm fairly stable on this combination, but my weight is a problem, and I'm concerned about it. When I was on 50 mcg of T3, my other symptoms (depression, anxiety, fatigue, muscle pain, hair falling out, poor concentration, insomnia) cleared up. My weight also fell back to normal, and I maintained the lower weight. But this time, after my episode of hypothyroidism, my weight hasn't come back down. This is troubling because I follow an excellent health program. I eat a perfect diet, take nutritional supplements, and I've done practically every healing regimen in the natural medicine world. I exercise very hard with weights and cardio—one hour in the morning four-to-five days a week. Then I do a very brisk walk for an hour most evenings. Despite this regimen, I'm in constant pain. And my weight has stayed higher than normal. I have a layer of fluidy, fatty, flabby, cellulite type of fat over my arms, belly, thighs, and butt. It doesn't seem to shift no matter how hard I exercise. Is it possible that I need more T3 to get rid of the pain and flab? I love your work. Thank you in anticipation of your reply.

Dr. Lowe: I am sorry you've had the health problems you describe. Whenever I hear from a clinician such as you, I regret even more the confusion that reigns in the field of clinical thyroidology. You're by far not the only clinician perplexed about how to use thyroid hormone effectively to alleviate problems such as your pain and fat.

When you went through the severally stressful time you mentioned, you most likely needed to temporarily increase your cortisol dosage rather than your T3 dosage. And by increasing your T3 dosage, you may have worsened the cortisol deficiency induced by the stress.

When the adrenal cortices are functioning well, stress causes them to substantially increase their secretion of cortisol. In my opinion, during stress, the person on physiologic cortisol therapy, as you're on, should mimic what the adrenal cortices do during stress. The person should take more cortisol than during tranquil times.

During the stressful time you experienced, it's highly likely that your need for cortisol markedly increased. By increasing your T3 dosage, you may have sped up the clearance of cortisol through your liver. This would have decreased the cortisol available to your cells at a time when you needed much more than usual. You said that at this time, you again developed symptoms of hypothyroidism. It's possible that the symptoms were actually those of a cortisol deficiency. That's likely if the hypothyroid-like symptoms included fatigue, muscle weakness, lower tolerance of stress, and low blood pressure upon standing up.

Armour works well when the patient takes a high-enough dosage. It's possible, however, that you aren't taking enough. On your dosage of 4 grains, you're getting 36 mcg of T3. This is only 4 mcg less than when you felt well and stable on 50 mcg. However, the difference may be substantial for you as an individual.

The problem I see in cases such as yours is a black hole of sorts: how much of the T4 in the Armour (152 mcg in the 4 grains) do you absorb and convert to T3? We don't know. Some studies indicate that while we absorb almost 100% of T3, we absorb variable amounts of T4, for example 80% or 85%. But how much of it ends up converted to T3 and bound to T3-receptors is a mystery. Because we never know how much T4 is effectively used by one's body, I believe that using T3 is preferable. The relationship between symptoms or symptom relief and the T3 dosage is far clearer than with T4. More T3 dosage might also reduce or relieve your pain by inhibiting substance P production, by repressing the preprotachykinin-A gene, which codes for both substance P and its receptor.[1,p.732]

I hope, doctor, that you're soon able to relieve your pain and lose your excess fat. I suspect that you can do so by raising your T3 dosage a small amount. Also, if you experience any prolonged or intense stress, I hope you'll consider that temporarily increasing your cortisol dosage is the proper course of action.

Reference

1. Lowe, J.C.: *The Metabolic Treatment of Fibromyalgia*. Boulder, McDowell Publishing Co., 2000.

More on the Endocrinology Specialty's *Presumption* that T3 Adversely Affects the Heart

February 22, 2007
Question: My doctor diagnosed low cortisol and has me taking 20 mg of cortisol each day. I am concerned about taking too much, but she told me that 20 mg is a safe dose. What are the symptoms of too much cortisol so that I can watch for them? How much cortisol is too much?

Dr. Lowe: I have included below a list of the symptoms, signs, and test results when patients have severe excess cortisol. Keep in mind that factors other than excess cortisol can cause most of these symptoms, signs, and test results. Because of this, just because you have one or more of these features doesn't necessarily mean you're

taking Armour. Forest also found a French study that discussed a correlation between hyperthyroidism and joint pain. My endocrinologist is going to let me try a combination of Synthroid and Cytomel. If the combination gets rid of my symptoms and I don't develop joint pain again, we'll know it was the Armour that caused the pain. Maybe I had an allergy to Armour. What do you think about all this?

Dr. Lowe: It's within the realm of possibility that a patient could have joint pain as part of an allergy to some chemical constituent of Armour. But I seriously doubt that this was the mechanism of your joint pain.

The most likely mechanism is a cortisol deficiency stimulated by an effective dose of Armour. An effective dose of thyroid hormone increases the metabolism of the liver. Increased liver metabolism speeds the rate at which the liver clears various hormones, such as cortisol, from the blood. If the patient's adrenal cortices aren't capable of increasing their production of cortisol, the patient can develop a cortisol deficiency. Cortisol is an inflammatory hormone, and a deficiency of it can cause some tissues to easily become inflamed. Joints are highly susceptible to inflammation during a cortisol deficiency. The reason is that they're often subjected to mechanical stresses, such a movement and pressure.

If a cortisol deficiency was the mechanism of your joint pain, I would expect an effective dose of combined Synthroid and Cytomel (or Paddock's generic T3 in the US or Grossman's Cytomel from Mexico) to induce the pain again. To validly test for this mechanism, you should use the same ratio of T4 to T3 as in Armour (a 4-to-1 ratio). You should also take as much T4 and T3 as you were getting in the dose of Armour when the pain occurred.

If the pain reappears while you're using Synthroid and Cytomel, your next step should be adrenocortical testing. You should get several measures of your salivary cortisol through a 24-hour period. Possibly, you should also undergo an ACTH-stimulation test. In that test, you'll have an injection of ACTH, and the change in your cortisol level will be measured. You should, of course, still be using Synthroid and Cytomel when you undergo the testing.

Your endocrinologist may order or perform the ACTH test. However, most conventional doctors still don't test for levels of cortisol in saliva. If your endocrinologist isn't familiar with the saliva test, we'll be happy to order it for you. If we can help, phone us at 303-413-6003, or write to Tammy Lowe at Tammy@drlowe.com.

Tammy@drlowe.com

Our Educational Consulting Service

We provide educational consulting to both patients and clinicians. Phone us at 603-391-6061, or preferably, write to us at Tammy@drlowe.com. Our fax number is 303-496-6200. ***—Tammy Lowe***

taking too much cortisol.

Also bear in mind that what is too much cortisol for a patient is an individual matter: What is too much for one patient may be too little for another, and vice versa. Moreover, some patients' tissues are partially resistant to cortisol, and they have to maintain a higher body level of cortisol than others to be free from cortisol deficiency symptoms and signs. Cortisol resistance is now a scientifically established disorder, but I don't believe researchers have established the incidence in the population. If a patient suspects he has cortisol resistance, it is crucial that he work with a doctor who is knowledgeable about the disorder and experienced in working with cortisol resistance patients.

My treatment team has worked with some patients who over medicated themselves with cortisol. The patients developed the symptoms and signs of cortisol excess only after several months of taking very large daily doses—several times the 20 mg you're taking.

As I said, though, how patients respond to different doses of cortisol is an individual matter. Because of this, it's hard to say what will be excessive for any particular patient. However, it is important for patients to stay within the range considered "physiologic" rather than "pharmacologic."

"Pharmacologic" refers to the large doses of cortisol analogues (such as prednisone) that doctors use—hopefully briefly—to suppress inflammation. Pharmacologic doses are often used to treat conditions such as severe acute asthma.

"Physiologic" refers to maintaining a body level of cortisol that the adrenal cortices would maintain, were they capable of doing so. One aim, then, of physiologic cortisol therapy is to give the patient just enough cortisol to make up for what his adrenal cortices should be but aren't providing.

Because of individual variability, it's best for each patient to work with a knowledgeable doctor to decide what is for that patient a physiologic dose. But I agree with your doctor: your dosage of 20 mg is mostly likely well within the harmless physiologic range.

Symptoms, Signs, and Test Results in Cortisol Excess

O Weakness
O Muscle wasting
O Poor wound healing
O Obesity of the trunk of the body
O Fat pads above the collar bones
O Skin that is thin and atropic
O Rounded "moon" face
O Psychological disturbance such as mood swings
O Glucose intolerance
O Kidney stones
O Osteoporosis
O Reduced resistance to infection
O Edema
O Easy bruising
O Purple striae (stripes) on the abdomen
O Fat collection at the junction of the back of neck and upper back ("buffalo hump")
O Plethoric (overfull, turgid, inflated) appearance
O High sodium & low potassium levels
O Slender arms and fingers and legs and toes
O Excessive hair growth (hirshutism)
O Menstrual irregularities such as amenorrhoea (absence of periods)
O High blood pressure

—Continued at top of right column

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Q&As

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Thyroid & Fibromyalgia in the UK

November 15, 2009
Dr. John C. Lowe
Director of Research

Question: I'm so happy to have found your website. I've had hypothyroidism for 2 years. I'm 61 years old and am on 125 mcg of thyroxine. Over the last 6 months, I've developed pain and weakness in my thigh and upper arms muscles. I also have inflammation of my Achilles tendon, my the tendons in my feet, knees, elbows. I have all 18 tender points. I've been pushed from pillar-to-post and finally was told I have fibromyalgia. I was also told my thyroid test results show normal. However after reading your information on the link between thyroid and fibromyalgia, I'm wondered if you can suggest what to I ask my doctor so he'll test me for thyroid resistance. I'm due to see him on Monday and as I live in the UK and can't visit your organisation, I thought it would help if I told him about your research. I have loads of blood test results that all say I'm normal, but I definitely know these symptoms aren't in my mind. A rheumatologist has recommended a trial of pregabalin or amitriptyline which I don't want to take. Is there another thyroid test which might point my doctor to try and see if I am thyroid resistant. Thank you so much for reading my email.

Dr. Lowe: Your description of your plight indicates that you are one of the millions of people being victimized by Big Pharma and the conventional medical system it uses to ensnare people. I think you're wise in not wanting to use pregabalin, amitriptyline, or any of the other drugs being pandered to people whose doctors diagnose them as having "fibromyalgia." I've never heard of a patient getting well with any of the so-called "fibromyalgia drugs," and many people have such bad reactions to them that they have to give them up.

The vast majority of people who meet the criteria for fibromyalgia have too little thyroid hormone regulation, and that is likely to be the case with you. Unfortunately, you may not be able to convince conventional doctors in the UK that you need a trial of thyroid hormone therapy. Even if you could, they most likely would restrict you to T4 replacement. With that therapeutic approach, you probably wouldn't fair any better than you do now. Because of that, you'll probably do best by contact the good people at Thyroid UK. They are aware that inadequate thyroid hormone regulation can cause the set of symptoms that lead to a diagnosis of fibromyalgia. And they can give you the contact information for doctors who will treat you with a therapy other than T4 replacement.

The contact page at the Thyroid UK website is: http://www.thyroiduk.org/. The organization's other contact information is below:

By Post:
Thyroid UK
32 Darcy Road
St Osyth
Clacton On Sea
Essex
CO16 8QF By Phone: 01255 820407

When you do undergo a trial of thyroid hormone therapy, you might mention something to the doctor: that is, that I described to you the protocol that in my experience has worked best for most fibromyalgia patients. I'll give you a brief overview.

You may be hypothyroid, and if so, you're likely to improve with Nature-Throid. This product contains both T4 and T3. Most patients begin with 1 grain and at 3-week intervals increase their dosages until they get satisfactory results. Most patients have to slightly suppress their TSH levels before they begin to improve. Except in the rarest of cases, TSH-suppressive doses are harmless; this is evidenced from the hundreds of thousands of thyroid cancer patients who live in good health with suppressed TSH levels.

If you reach a dosage of 4 grains of Nature-Throid and haven't improved, that's the time to consider that you may be thyroid hormone resistant. If you are, you'll mostly likely have to use plain T3 to recover your health. Sustained-release T3 usually doesn't work as well as plain T3.

The doctor you work with may be concerned about your cardiac health. If so, ask him to order ECGs each time before you increase you dose of thyroid hormone. If your doctor needs more assurance that your cardiovascular system is healthy, he or she can also order more extensive cardiac evaluations.

If the doctor wants to learn the details of the treatment protocol that our studiesshow works best, I recommend that he or she get a copy of my book The MetabolicTreatment of Fibromyalgia. It is available at www.McDowellPublishing.com. Or he or she might get a copy of the protocol chapter (Chapter 5.2) from the book. It's available at the publisher's e-chapters page: www.mcdowellpublishing.com/echapters/contents.htm.

I hope you persist, Ann, until you find a doctor in the UK who'll help you go through a trial of thyroid hormone therapy other than T4 replacement. Please let us know how you do.

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Thank You For Your Continuing
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Thyroid Science
An open-access journal for truth in
thyroid science and thyroid clinical practice

Remainder

Replay is Available!

Bette Dowdell of TooPoopedToParticipate.com here.

Welcome to the replay of Dr. John C. Lowe answering listener's questions about the thyroid, fibromyalgia, etc.

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Get Dr. Lowe's newsl

- Get Bette's free health e-zine
- Free chapter of Pep for the Poop

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Newsletter from Dr. John C. Lowe, LLC

Thyroid & Metabolic Research and Educational Consulting — *Sept. 12, 2010*

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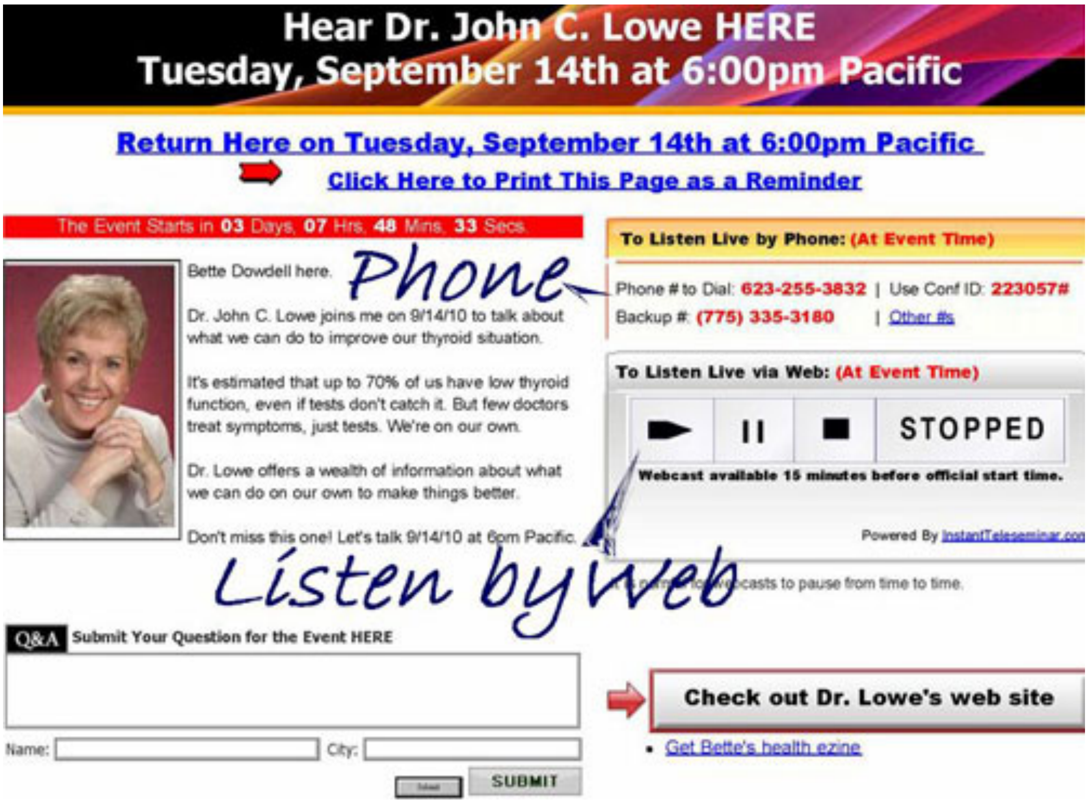
www.drlowe.com (603) 391-6061 Tammy@drlowe.com

Bette Dowdell & Dr. Lowe: Live Teleseminar this Coming Tuesday Night

Dr. John C. Lowe

On Tuesday, September 14, 2010, I'll be the guest on Bette Dowdell's teleseminar. She and I invite you to listen in live.

I know that many of you are already familiar of Bette's popular website Too Pooped to Participate. She often sends out her free e-zine and she offers her e-books such as Pep for the Pooped. I admire Bette partly because she's generously passed forward to others-in-need what she learned in recovering her own health after conventional medicine failed her.



Hear Dr. John C. Lowe HERE
Tuesday, September 14th at 6:00pm Pacific

Return Here on Tuesday, September 14th at 6:00pm Pacific

Click Here to Print This Page as a Reminder

The Event Starts in **03** Days, **07** Hrs, **48** Mins, **33** Secs

Bette Dowdell here.

Dr. John C. Lowe joins me on 9/14/10 to talk about what we can do to improve our thyroid situation.

It's estimated that up to 70% of us have low thyroid function, even if tests don't catch it. But few doctors treat symptoms, just tests. We're on our own.

Dr. Lowe offers a wealth of information about what we can do on our own to make things better.

Don't miss this one! Let's talk 9/14/10 at 6pm Pacific.

To Listen Live by Phone: (At Event Time)

Phone # to Dial: **623-255-3832** | Use Conf ID: **223057#**
Backup #: **(775) 335-3180** | Other #s

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Q&A Submit Your Question for the Event HERE

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When you reach the page, either use the phone number or click the go arrow to listen by web on your computer. The whole picture above of Bette's teleseminar page is a link, so if you want, just click anywhere on the picture.

By the way, you may not have the latest version of Adobe Flash Player on your computer. Adobe provides the latest version for *free*. You can easily download it:

http://www.adobe.com/software/flash/about/. Click the orange button that reads, "Install NOW: It's free."

Submit a Question. If you want, submit questions in between now and the teleseminar on Tuesday evening. At Bette's teleseminar webpage, you see a "Q&A" box at the lower left of the page, which you can see in the picture above of her webpage.

Once Again. You can listen live during the teleseminar by telephone or through your computer.

(1) **Webpage**. Bette's teleseminar webpage: http://budurl.com/t7xs.

(2) **Listen by Phone**. The phone number to call is *623-255-3832*. (The backup phone # is 775-335-3180.) You'll also need the conference ID, *223057#*, which is also at available on her teleseminar webpage.

(3) **Listen by Computer**. Just click on the go arrow (see our copy of Bette's webpage above.)

(4) **Date**. The date is this coming Tuesday, September 14th.

(5) **Time**. The time is 6:00 pm Pacific Time. That's the same as 7:00 pm Mountain Time, 8:00 pm Central Time, and 9 pm Eastern Time.)

(6) Please call in a few minutes early so I know you're there. Please do not give this code to anybody else.

John C Lowe

Tammy@drlowe.com

Our Educational Consulting Service

We provide educational consulting to both patients and clinicians. Phone us at 603-391-6061, or preferably, write to us at Tammy@drlowe.com. Our fax number is 303-496-6200.

—Tammy Lowe

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Thyroid Science

A journal dedicated to truth in thyroid science and thyroid clinical practice

Thyroid Science 1(1):C1-21, 2006

Thyroid Hormone Replacement Therapies: Ineffective and Harmful for Many Hypothyroid Patients*

(Full Text Free in pdf format)

Dr. John C. Lowe*

*drlowe.com, FibromyalgiaResearch.org
drlowe@drlowe.com, drlowe@FibromyalgiaResearch.org

Selected Response Letters

The document this page introduces is a formal critique by Dr. John C. Lowe. In it, he presents documentary evidence for the ineffectiveness and harm of thyroid hormone replacement for many hypothyroid patients.

The studies he critiques show that two studied types of replacement therapies were ineffective for many patients. Other studies, which Dr. Lowe cites, also show that patients using T4-replacement have an increased incidence of other diseases associated with hypothyroidism, and increased chronic use of drugs to control the symptoms of persisting hypothyroidism and those of other diseases.

Citation: Lowe. J.C.: Thyroid hormone replacement therapies: Ineffective and harmful for many hypothyroid patients. *Thyroid Science,* 1(1):C1-21, 2006.*

(*Originally published at www.drlowe.com and www.FibromyalgiaResearch.org, May 4, 2004.)

(**Full Text Free** in pdf format)

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Help Stop the Thyroid Madness & Mayhem

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| An urgent appeal to help stop the thyroid madness |
| My answer to Natalie |
| Ordering your own lab tests at the lowest possible fees |

An Email from Natalie & an Urgent Appeal to Stop the Thyroid Madness & Mayhem

I awoke this morning, and, as I often do, I read the first several of the hundred or so emails that came into my mailbox during the night. The first of the emails, from Natalie, outrage me. Not at Natalie, I hastily add! But to something she wrote about that makes my blood temporarily boil. It's something I *vehemently* want to help bring to an end.

That something is the persecution of different medical specialists for a specific reason: because they've gained attention for helping patients. The problem with the clinicians helping the patients is that they did so with methods that fail to meet one criteria—contributing money through drug or test sales that further fatten the already bloated bank accounts of the corporations that share the booty with the specialty of which the clinician is a member.

Through intimidation by the endocrinology specialty, and by insurance company dictates, hypothyroid and thyroid resistance patients figuratively live in concentration camps of ill health and premature death. Their lives are painful, dreary, and miserable, all for the sake of power and profit for others.

This persecution happens in most medical specialties. But I think it most often happens in a particular areas of medical practice: that in which clinicians realize that T4 replacement is an inferior therapy, and so they use T3 along or with T4, which brings them to the attention of local thug endocrinologists. The endocrinologists the file complaints against the clinicians with medical regulatory boards.

This example Natalie gives in her email involves a cardiologist. He's far from the only cardiologist I've learned of being persecuted for not contributing to the choices in concepts and treatments. This case, however, is emblematic of what often happens to clinicians who care for thyroid patients. Because of that, I use it to open this article.

> Subject: Cardiac doc stops his practice
> From: "Natalie" <XXXX@XXX.com>
> Date: Wed, January 26, 2011 12:52 pm
> To: drlowe@drlowe.com
>
> Dear Dr Lowe,
>
> You may already know about Dr Lundell, but he's in your league—forced to give up his practice to speak the truth. I think you guys should band together and have a conference, no matter what one's specialty is. As you say, the Big Pharma/FDA collusion and corruption is criminal!
>
> Natalie
>
> * * * * * * * * * * * * * * * *
>
> Dr.Lundell's story is at these this website:
>
> http://www.spacedoc.net/statin_scam
>
> **Dr. Lundell's Conclusion in the Article:**
>
> "In spite of being Chief of Staff and Chief of Surgery at a large specialty heart hospital, I found that I could not change medicine no matter how much I preached and pleaded, no matter how much scientific evidence I gathered that cholesterol

My Answer to Natalie

Subject: Thank you so much per Dr. Lundell
From: "Dr. John C. Lowe" <drlowe@drlowe.com>
Date: Sun, January 30, 2011 7:46 am
To: XXX@XXX.com

Dear Natalie,

Thanks you so much for sending the email below to me. I'm outraged by this report and your email has inspired me to send out another email this morning. When you read it, you'll recognize it, but it may be edited a bit. Thank you, thank you, thank you. As you'll see in my final comments, I sincerely hope you become a thyroid patient advocate. It's quick and easy, and numbers count so dearly. My sincerest gratitude for sharing the piece on Dr. Lundell with me.

Dr. Lundell isn't the first cardiologist I know of who was either run out of town or lost his or her license to practice medicine for focusing on underlying inflammation as the main disease-producing mechanism of atherosclerosis and coronary disease. It used to be said of such unjustly persecuted doctors, "They were just ahead of their time." That's true in that these doctors were right; it's just that their arrogant, dogmatic, and retaliatory colleagues who persecuted them eventually came to believe and even practice exactly what they formerly persecuted few who had keen and human-helping foresight.

History is full of such examples, and it appears to me to go back to the old heard mentality of the medical profession. An ancient medical mantra is, "Be not the first to by whom the new is tried, nor the last to lay the old aside." I know of some doctors who've actually thought this wise advise, and it is if you want to avoid persecution by your heard-mentality colleagues. But to follow the advice is to stagnate in current "knowledge" and forgo pursuit of what may better health ailing human beings.

I believe the heard mentality is greatest within the endocrinology specialty. When in the US, the Abbott Laboratories and other members of Big Pharma occasionally give the Association of Clinician Endocrinologists a million dollars (that's right, $1,000,000) as an "unrestricted grant," and the fact being that he who pays the piper calls the turn, it's my personal opinion, back by substantial evidence, that the endocrinology specialty has been bought off, and their heard mentality is for the purpose of persecuting foresighted and wayward clinicians as a *quid pro quo* for the huge payoff they've gotten from Abbott and other corporations.

Please sign up with us *anonymously*. That way, we'll know about how many people will so to be counted when we call the endocrinology specialty and others for harm at that hands. Please sign up at each of these two sites:

worldthyroidregister.com

tpa-uk.org.uk/register_of_counterexamples.php

In other words, to them, it's, "To hell with the health and well-being of patients; we've got huge financial incentives to keep pretending that T4 replacement and the ordering of millions of TSH assays (from which the corporations benefit) guarantees a flow of money that's simply too good to be interrupted by people with a sentimental, tree-hugging attitude toward the patients we forfeit for all the financial perks."

Sad, but alas, *true*! We *must* stop this "thyroid madness," to use Janie Bowthorpe's well-picked words. And we *must* stop the worldwide mayhem.

The financial venture of the Endo/Corp Cartel must be brought to an end. To this end, I ask you to consider taking two actions. These will take very little time and effort. I will soon be writing extensively on these two actions, as I believe that finally, those with organizational abilities have taken the lead in organizing mass action against the Cartel, and I'll joyously serve by letting more and more people know that they can take part simply through anonymously giving their email address pidpipper for this world-benefitting humanitarian cause.

(1) Sign up at the website of Gordon Skinner, eminent UK virologist who studied fibromyalgia/chronic fatigue and learned that, instead of a viral infection, the condition(s) was caused by too little thyroid hormone regulation. Dr. Skinner has courageously stood tall as he was persecuted by the UK's General Medical Council (GMC). The GMC is a UK agency that presumably protects the UK population from unfit physicians. It serves, however, as a thug organization to shamelessly punish clinicians who gain a good reputation for rescuing patients

> was not a problem and that treating cholesterol with medications was counter productive.
>
> "So I made that difficult decision and left my successful surgical practice in order to have the freedom to speak, write, and teach the truth about heart disease. I wrote a book *The Cure for Heart Disease*, which explains that the real cause of heart disease is low grade inflammation. For without inflammation cholesterol would never accumulate in the wall of the blood vessel and cause plaque with its eventual consequence of heart attack and death.
>
> Dwight C. Lundell M.D.
> www.thecureforheartdisease.net
> Chief Medical Consultant, Asantae Inc.
> Chief Medical Consultant at www.realweight.com

My response to Natalie's emails is below and finishes in the top of the right column. I sympathize with the plight of Dr. Lundell. I do so because I, too, gave up my licenses because of harassment and threatened legal consequences.

I've known of doctors since the early 1970s whose licenses were revoked for them not playing along with ill-gotten-gains of T4 replacement. And I've know many other doctors who gave up their licenses voluntarily.

They gave up their licenses voluntarily to avoid draining legal fees. You see, this is one of the underhanded tricks of thugs within the endocrinology specialty. Their actions, to me, betray their thoughts: "Fight us in court and other hearings to try and keep your license, and we'll use taxpayers money for lawyers who'll bankrupt you with legal fees. Then, without two pennies to rub together, we'll have closed your big mouth for good about the highly-profitable financial venture we have going with Big Pharma."

I've long been advised by two groups of persecute clinicians. First is those who fought legally and lost all the had. The others are ones who, I think, wisely voluntarily handed over my licenses and were thereby freed to go on fighting for right with the thugs in endocrinology specialty. I took the latter path. By doing so, I took the cross-hairs off my forehead, and defrocked of my licenses, I'm now free to say anything I want that doesn't violate libel or slander laws, which unfortunately for my opponents, I understand quite well.

I've long said to those opponents, "Go ahead and deprive e of my license to practice. Do that and you'll free me from the all-consuming time demands of clinical practice. Then I'll have plenty of time to invest my energy in come after you unscrupulous bastards. And if I don't die first, one-way-or-another, I'll bringing down your profitable misery-making T4 replacement empire."

Well, here I am now, free to fight in ways that licenses long restrain me from. And if I haven't started before now, my reply to Natalie begins my campaign to destroy the money-making, misery-creating scheme of what I call the Endo/Corp Cartel, a rotten enterprise that makes the drug war at the US/Mexico border look like kids making and throwing mud cakes in a toy box. My Answer to Natalie.

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Tammy@drlowe.com

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We provide educational consulting to both patients and clinicians. Phone us at 603-391-6061, or preferably, write to us at Tammy@drlowe.com. Our Efax number is 303-496-6200. —***Tammy Lowe***

The gold standard among
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whose lives have been ruined T4 replacement. By signing up with your email address at Dr. Skinner's website, you'll be letting us know that you oppose the life-ruining atrocities of the GMC and what I call the Endo/Corp Cartel, which to me is as bad in effect upon humanity as the Mexican drugs cartels at the US/Mexico border.

All you need to do is sigh up completely anonymously. It's the number of people we know who side with use that's important. The web address is: worldthyroidregister.com

(2) Go to the website of The UK Charity, "Thyroid Patient Advocacy." The charity groups website is www.tpa-uk.org.uk is. This charity has created a World Register of Counterexamples to levothyroxine-only (T4) therapy. You are a counterexamples if (a) you've continued to continued to suffer from hypothyroid symptoms on T4-only therapy, and (b) your symptoms disappeared once they were started on a thyroid hormone product that contained T3. It doesn't matter whether the T3-containing product was synthetic or a natural thyroid product. The objective of this Register of Counterexamples is to draw to the attention of those responsible authorities throughout the world. The motive behind the charities' Register is the dire need for an urgent unbiased reexamination of the methods for diagnosing and managing the symptoms of hypothyroidism.

If you failed to benefit from T4 alone but then benefitted from a product that contained T4/T3 or T3 alone, you quality as a counter example. As Sheila Turner, head of the charity wrote, "Please complete the 3 questions with either 'YES', 'NO' or N/A. You can do that quickly at tpa-uk.org.uk/register_of_counterexamples.php. All responses will be collated online, and your email address (if you provide one) will be used *only* to contact you at a later date should this be becomes necessary. All the best to your and your loved ones."

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Yours sincerely,
Dr. John C. Lowe
Director of Research: Fibromyalgia Research Foundation
FibromyalgiaResearch.org
Editor-in-Chief: Thyroid Science
thyroidscience.com/
(603) 391-6060 (603) 391-6061
drlowe@drlowe.com Tammy@drlowe.com
www.drlowe@drlowe.com

How to Order Your Own Lab Tests at the Lowest Possible Cost

Tammy Lowe

Above this short article, you can see the link for our clients to order lab tests through Direct Labs. We made special arrangements with Direct Labs to give our clients especially low fees for most of the tests they order. The discounted fees are available to clients when they use our special link, directlabs.com/drlowe.

Our clients can save money by using our link to Direct Labs, but you may be able to save even more by checking the fees for the tests you order for yourself at different labs. For example, I've found that PersonalLabs.com charges less for some of the most common tests we suggest but they also charge more for other tests that may be equally important. My husband and I feel that it is important to shop around to ensure that you are getting the price that is appropriate for your own budgetary need.

We have provided a short table of various lab tests and the cost associated with them through popular online laboratories. These labs are personallabs.com/, directlabs.com/drlowe, and privatemdlabs.com/.
We're dedicated to helping you and our other subscribers save in health care, whether you are guiding your own care or working with a clinician. If you know of labs that charge even less than the three labs I've included in the table, please let me know. We'll pass the information along to our other subscribers.

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Thyroid Science

A journal dedicated to truth in thyroid science and thyroid clinical practice

| Submission Methods | Types of Manuscripts |
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Authors' Guidelines

Below are general guidelines for a variety of types of submissions to *Thyroid Science*. We are committed to keeping the format and content of *Thyroid Science* typical of most scholarly journals. However, we do not want our guidelines to appear so rigorous and draconian that they drive away contributors. Authors who have previously published in journals will not have difficulty adapting their submissions to our guidelines. Those who have not previously published can adapt their manuscripts to our guidelines by reading the relevant guidelines and using as models letters or papers already published in *Thyroid Science*.

It is our policy to follow the exemplary example of the late Dr. David Horribin, Editor-in-Chief of *Medical Hypotheses.* His policy was to reject the *ad hominem* practice of most medical journals. That practice, which is by definition irrational, involves valuing *who* submits a manuscript over the *merit* of the manuscript's content. This practice places fraternal loyalty (a euphemism for "good-ol'-boyism") over truth seeking. The practice is an obstacle to the advance of science, for as history has shown, great advances in particular scientific fields have often come from the fresh, parallactic views of individuals outside that field. Hence, we, like Dr. Horribin, could not care less what a contributor's credentials are, or whether in fact he or she has a formal credential. What is important in *Thyroid Science* is reason and the pursuit of truth in thyroid science and thyroid clinical practice.

Submission Methods

Authors may submit manuscripts and related materials by snail mail, but we prefer electronic submission. Most authors submit their materials by email to Editor@ThyroidScience.com, attaching files prepared in a word processor. Most authors submit either Word or WordPerfect files. We prefer WordPerfect files, but Word files are acceptable—*with one exception*:

"docx" format. *We do not accept files in docx format*. This format is associated with Microsoft Word in Vista and subsequent Word versions. Files saved in this format cannot be opened by any previous version of Microsoft Word. Our security consultant believes that the free downloadable patch provided by MicroSoft to open docx files in Windows XP and previous versions of Windows contains MicroSoft malware coding that may interfere with our publishing software. In addition, it is our opinion that the creation of the docx format was a contrived effort by Microsoft to coerce Windows users who want to open docx files to purchase special software from Microsoft. We believe that refusing to cooperate with one more Microsoft-scheme-of-greed may help to dissuade the company from future superficial attempts to financially exploit its customers.

Types of Manuscripts

Criticisms | Clinical Cases | Debate | Editorials | Hypotheses | Reviews | Studies | Letters

Criticism Papers. In criticism papers, the author addresses an idea, opinion, belief, or hypothesis. For the purposes of criticism, all of these are called "propositions." A proposition is a statement that we can either affirm or deny, thereby characterizing it as either true or false. The process of criticism involves evaluating the full available evidence relevant to the proposition at issue. The intention should be to arrive at a conclusion that the evidence shows the proposition to be true or false.

Clinical Case Reports. Clinical case reports are for an author to report unusual findings, new treatments, or new uses of a treatment. These reports are intended to have heuristic value, serving to stimulate interest among patients, clinicians, or researchers. Such reports may lead other clinicians and/or researchers to confute or confirm the report. If confirmed, the author's initial report may turn out to be a major contribution to the field.

Clinical case reports seem especially important for sharing different treatment protocols for hypothyroid or thyroid hormone resistant patients. Today's conventional thyroid hormone therapy, T4-replacement, has been documented to be ineffective and harmful to many patients. Resistance to abandoning T4-replacement, or limiting its use to particular appropriate cases, is strong. The strength of the resistance derives mainly from financial incentives from corporations, particularly to the endocrinology specialty. However, physicians in many countries are experimenting with different treatment protocols in their clinical practices. Many of these physicians keep a low profile to avoid retaliation by endocrinologists who may file complaints against them to medical regulatory boards. Because of this disgraceful and deplorable state of affairs, if an author/physician requests it, *Thyroid Science* will publish his or her clinical case paper anonymously.

Debate. Of all the types of submissions, our requirements for debate submissions are the least rigorous. However, the submitted paper should conform to our standard format. In general, you should include the following five components in your letters or papers of debate: (1) a statement of the issue you are debating; (2) the place where the issue you are debating was published; (3) a brief statement of your position on the issue, that is, whether you agree or disagree; (4) the evidence for your position; and (5) a clearly stated conclusion. Below is an example, with numbers inserted to show the necessary components of debate:

> *(2) In his June 6, 2006 letter to* Thyroid Science*, (1) Dr. Mark Weed argued that the best measure of a patient's metabolic rate is his or her TSH level. (3) I am baffled by Dr. Weed's public expression of such as easily refutable notion. At most, we might consider the TSH level a measure of the metabolism of the thyrotroph cells of the anterior pituitary gland, but even that is a stretch of the imagination. (4) To suggest that the TSH is a reliable gauge of the metabolism of any other tissue is totally without experimental support. I challenge Dr. Weed to cite a single study showing that the TSH* reliably *correlates with legitimate measures of the metabolic rate, such as calorimetry. In fact, as the references I cite below demonstrate, studies have failed to show enough of a correlation between the TSH and the resting metabolic rate for the TSH to be of* any *clinical use in finding a thyroid hormone dosage that gives patients normal metabolic rates. (5) Therefore, not only is the TSH level not the best way to measure a patient's metabolic rate; it in fact doesn't measure it at all.*

We must make a point emphatically about debating: As wicked a person as your opponent may in fact be, attacking him or her personally may constitute libel. Because of this, you must deal *strictly* with his or her beliefs, opinions, propositions, or hypotheses—*not* him or her personally.

Editorials. An editorial is simply the expression of someone's opinion. When one of our editors or review board members gives his or her opinion in *Thyroid Science*, we classify it as an "Editorial." We classify an editorial as a "Guest Editorial" when we requested that someone outside *Thyroid Science* write it for us, or when the someone else submitted the editorial without our solicitation.

An aim of *Thyroid Science* is reason and scholarship. In an editorial, however, the author may utter any nonsensical or scientifically-unsupported dogmatic belief he or she wishes—as long as he or she doesn't libelously attack another person, and as long as the nonsense or dogmatism is relevant to the science or clinical practice of thyroidology. Of course, we *encourage* anyone who writes an editorial for *Thyroid Science* to be reasonable in expressing his or her beliefs, appraisals, and judgments. By "reasonable," we mean that an author presents relevant evidence for his or her opinions. But alas, by definition, an editorial is the expression of an opinion! So if an author so wishes, he or she can, without a dab of evidence, simply say "Here is what I believe."

Hypothesis Papers. The standards for hypothesis papers are more flexible than for those for original studies and reviews. In hypothesis papers, you may be more flexible and original in your use of literary methods, techniques of presentation, or information, if you believe these enable you to better express your thesis. However, you must uphold a high standard of scholarship by basing your hypothesis on relevant evidence.

Reviews. Review papers are strictly evidence based. They must be referenced with citations from the area of research they address. In review papers, the author may evaluate the available evidence and describe the state of the area of research based on the evidence or the author's evaluation of that evidence. The author should include any tables or figures that support his or her conclusion(s). If the tables or figures have been published before, the author must secure written permission to reprint them and provide *Thyroid Science* with a copies.

Reports of Original Studies. Reports of original studies must contain the following sections:

Abstract | Introduction | Materials and Methods | Results
Discussion | Acknowledgments | References | Tables and Figures

Abstract. The Abstract should state with 250 words: (1) The problem that was studied. (2) The hypothesis tested. (4) Methods used. (5) Results of the study. (6) Conclusion(s) based on the results. (7) Ten or fewer key words (these will be used by our website search engine and by abstract indexing services).

Introduction. The Introduction should include a relevant literature review, a description of the problem studied, and the hypothesis that was tested.

Materials and Methods. In this section, the author(s) should describe study subjects, inclusion and exclusion criteria for subjects, and the protocol for processing subjects during the study. The protocol should be described clearly enough so that other researchers can use the description to replicate the study. The author(s) should describe any equipment used, including brand names, the marketing companies, and the cities, states, and countries in which the companies operate. The statistical tests used should be listed in a separate subsection of this section titled "Statistical Analysis."

Results. In this section, authors should describe the results of the tests conducted in the study. The results should be stated in terms of the outcome of statistical analyses. Conclusions should not be included in this section.

Discussion. Authors should describe the relevance of your study findings in terms of the specific hypothesis they tested. The discussion should also related the findings to any area of the field of thyroidology that is relevant. When the authors state opinions, they should concede this. Other types of statements should be justified based on previous studies or published evidence. The discussion should end with any limitations to the study that the authors are aware of.

Acknowledgments. Any person, group, or organization that contributed to the study but does not warrant authorship can be cited in this section.

References. Each reference referred to in the text of the paper should be give a number in brackets. The reference should be listed in the References section by that number. In the text of the paper, reference numbers do not have to appear in sequence. References do not have to be listed in the References section in alphabetical order. We strongly encourage authors to refer to and use the format of previous papers published in *Thyroid Science* and adapt their papers to that format. Journal and book titles should be in italics. The paragraph below shows how references should be place within the text of the paper:

> "Although clinicians commonly state that transthyretin transports only T4 across the blood brain barrier,[1,2][6,p.39] the protein also transports T3[3,4] and other molecules, such as dioxins and PCBs.[7-9]" As Mason stated in his textbook *Thyroid Transport Proteins*, "Transthyretin is far from the an exclusive T4 transporter."[20,p.657-8]

Notice that brackets can appear within a sentence immediately following the statement they document. When brackets appear at the end of a sentence, the should follow the period. Authors can include two or more reference numbers separated by comma within brackets, but when a page number is give for a reference number, the reference and page numbers should be set off within brackets from other bracketed reference numbers.

Giving page numbers is not absolutely necessary, but we *strongly* prefer that authors include them whenever possible. The preference is in the vein of good scholarship. Their presence of page numbers will make it easier for readers to find the exact page in a journal or book where a statement is made or where a point is documented.

Authors should use the following format for listed papers and books.

Journal papers:

[One author] 1. Silva JE. Thyroid hormone control of thermogenesis and energy balance. *Thyroid*, 5:481-492, 1995.

[Two authors] 1. Kunos, G. and Ishac, E.J.N.: Mechanism of inverse regulation of α1- and β-adrenergic receptors. *Biochem. Pharmacol*., 36: 1185-1191, 1987.

[Three authors] 1. Geenen, R., Jacobs, J.W., and Bijlsma, J.W.: Evaluation and management of endocrine dysfunction in fibromyalgia. *Rheum. Dis. Clin. North Am*., 28(2):389-404, 2002.

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Thyroid Hormone & the Heart: Pounding Heart after Starting Thyroid Hormone

Contents of Thyro-Gold

September 15th, 2011

A question we often get is why Thyro-Gold contains the following ingredients. I've briefly explained why below.

- **Whole-gland thyroid powder** taken from pasture-fed New Zealand cows.

- **L-Aspartic acid**: Please bear in mind that aspartic acid and aspartate are NOT the synthetic sweetener "aspartame"! Aspartame is a laboratory-modified combination of the amino acids phenylalanine and aspartic acid and the alcohol methanol. Aspartame is a compound foreign to the human body and potentially harmful to human health. In stark contrast, aspartic acid and phenylalanine in their natural forms are made by the human body, are part of human diets, and they are necessary to human health, vitality, and well-being.

Thyro-Gold is included as a filler.

- ***Coleus Forskohlii*** that contains forscholin. This is a botanical that accelerates energy metabolism and the breakdown of triglycerides in the fat stores of the body.

- **Vegetable capsules**.

- **Rice powder**. To keep costs down for our customers, we switched from another botanical to rice powder, which is less expensive.

- **Silicon dioxide**. Silicon dioxide or silica is silicon, which is an element in the periodic table. Most of it is present on earth as silicon dioxide, which is silicon bound to oxygen. As such, it's called silicon oxides. Silicon makes up 26% of the earth's crust. The only more abundant element is oxygen. Examples are sand (silica), quartz, rock crystal, amethyst, agate, flint, jasper, and opal. Silicon oxides are also present in minerals, such as asbestos, feldspar, clay, and mica. Silicon is important in both plant and animal life. For example, algae extract silica from the water and incorporate it into their cell walls.

Workers who breathe in too much silicon dust may develop a serious lung disease known as "silicosis." People with diminished lung capacity, such as those with severe asthma, are especially vulnerable to inhaled silica.

However, silica appears to be harmless as a common additive in foods and dietary supplements. Food and supplement manufacturers add silica mainly to absorb water and make powdered foods flow.

Rarely someone claims to be allergic to silica. As the second most common element on earth, I believe such anecdotal reports to be highly inaccurate. Silica is virtually ubiquitous in our environment, and if one had an allergic reaction to silica, his or her exposure would be virtually unavoidable; he or she would would most likely have to live in a bubble container guaranteed to be free from silica, which would be almost as difficult as building a container of oxygen. I consider silica safe as a food and supplement additive.

Tammy@drlowe.com

Our Educational Consulting Service

We provide educational consulting. Phone us at 603-391-6061, or preferably, write to us at Tammy@drlowe.com. Our Efax number is 303-496-6200. —***Tammy Lowe***

Mercola/Lowe audio interview and downloadable transcript

The gold standard among

Pounding Heart

On Tuesday night, July 19th, Bette Dowdell and I had a teleseminar on thyroid hormone and the heart. (Teleseminar link: http://budurl.com/g52s) Unfortunately, a technical problem cut short our discussion, and we weren't able to cover the depth-and-breadth of the topic.

From the feedback we got, however, the topic is one of great concern to both patients and clinicians. Because of that, I'll be covering the topic over time in our newsletters. I'll also cover it in greater detail in our forthcoming book *Safely Getting Well with Thyroid Hormone*.

Main Point. My main point in Bette's and my discussion was this: Heart problems are typically not *caused* by thyroid hormone therapy; instead, they are *revealed* by it. The solution is hardly ever to give up thyroid hormone altogether—rather, it's to temporarily reduce one's dose of thyroid hormone until the person can correct the underlying problem that thyroid hormone has unveiled. Then the person can increase the dose to an optimal amount for him or her.

In this newsletter, I want to mention only one noteworthy point about heart health and thyroid hormone: that is, the heart *pounding* many people perceive once they begin to use a high-enough dose of thyroid hormone.

As far back as 25-years ago, my clinician/research team often heard patients express fear of the heart pounding. It usually began after we had switched the patients from namby-pamby T4 replacement to a more effect thyroid hormone therapy, and increased their doses high enough to start feeling some limited improvement. An occasional patient would ask, "Is this little bit of improvement worth damaging my heart?"

My colleagues and I hit the textbooks and spent many hours in the medical library tracking down and reading relevant study reports. What we learned is this: The pounding patients felt was *not* an abnormality. Our cardiac evaluations and those by cardiologists showed no abnormalities whatever. In fact, the pounding was a signal that the thyroid hormone therapy was beneficially affecting a patient's heart.

In hypothyroid people, the heart is under-stimulated by the sympathetic nervous system. The heart is also inhibited by the parasympathetic nervous system. (For those of you who have a copy of my book *The Metabolic Treatment of Fibromyalgia*, I explain this phenomenon in several chapters, especially Chapter 3.1.)

When the hypothyroid person begins to use an effective dose of thyroid hormone, the sympathetic nervous system increases its stimulation of the heart. The parasympathetic nervous system also ceases to inhibit the heart rate and force of contraction.

One result of this shift in stimulation of the heart is that the large chamber that propels blood out to the arteries (the left ventricle) contracts more forcefully. This is beneficial. The reason is that this delivers more freshly oxygenated blood to the arteries which deliver it to the brain and all other tissues.

For a short time, the more forceful propulsion of blood up out of the left ventricle against the aorta (the large caliber beginning of the arterial system) causes vibrations. Someone who has been hypothyroid is unaccustomed to feeling these vibrations. He or she therefore perceives the vibrations more intensely. It's a new experience that disturbs many of them, fearing that their hearts are dangerously over-stimulated. The fact is, however, that the patient's heart is finally healthily stimulated.

Most patients feel the pounding more intensely when lying in bed. This is expected in that the mattress serves as a sounding board. The mattress reflects back toward the person the vibrations from blood that is more forcefully ejected from the large chamber up against the inner lining of the aorta.

Of course, when it comes to the heart, it's best to consult a trusted clinician about a troubling heart-related experience. If the clinician isn't familiar with the newly-felt pounding, I suggest you let him or her read this brief article. There may be some doubt, of course, that your pounding is not merely a normal physiological response to effective thyroid hormone therapy. If so, ask your clinician to refer you for a comprehensive cardiologic evaluation.

However, having referred patients in my clinical days for countless cardiac consults, I remember only one patient whom a cardiologist didn't clear for thyroid hormone therapy. In this particular case, the cardiologist recommended that the *extremely* deconditioned patient undergo a course of cardiac rehabilitation and then resume her use of thyroid hormone therapy.

Finally, in most cases, the person who experiences the heart pounding desensitizes to it in a few weeks. He or she becomes accustomed to this normal stimulation of the heart. The vibrations simply become another unnoticed feature of the person's body function.

I hope this information is of help to some of you who may be concerned about the transient pounding from effective thyroid hormone

dietary desiccated thyroid products.
Franconia Ltd Nutraceuticals

therapy.

John C Lowe

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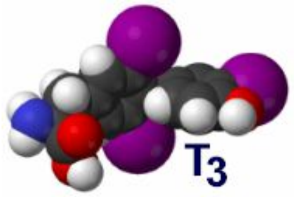

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Thyroid Science 5(9):1-7, 2010

T3-Induced Recovery from Fibromyalgia by a Hypothyroid Patient Resistant to T4 and Desiccated Thyroid*

(Full Text Free in pdf format)

Dr. John C. Lowe

Director of Research,
Fibromyalgia Research Foundation

Correspondence: Dr. John C. Lowe
drlowe@FibromyalgiaResearch.com, drlowe@drlowe.com
Tel: 603-391-6060 Fax: 303-496-6200
FibromyalgiaResearch.org, drlowe.com

*Originally published in the *J. Myofascial Ther*., 1(4):26-31, 1995. Reprinted with permission of McDowell Publishing Company, LLC.

Abstract to Case Report

The case report we present here was originally published in 1995. The case study was not blinded, but it was *highly* systematic. Three clinicians (a neuropsychiatrist; a physical therapist; and myself, a chiropractic physician) working in our separate clinical practices in different locations, evaluated the patient using objective measures. The data that I presented in the report of this case report fifteen years ago, and again now, was collected by the three independent clinicians each of whom worked simultaneously with the patient.

This systematic single case shows three noteworthy features of the patient: First, she was hypothyroid; second, she met the American College of Rheumatology criteria for fibromyalgia; and third, she no longer met those criteria and fully recovered when we switched her to T3 therapy after T4 and desiccated thyroid had failed to benefit her. It is worth emphasizing that the patient continued to meet the criteria for fibromyalgia when being treated with T4 (Synthroid) and then with desiccated thyroid (Armour). However, she quickly and dramatically recovered—no longer meeting the criteria for fibromyalgia—when we switched her treatment to plain T3 (Cytomel) with her daily dose well within the physiologic range.

I asked that *Thyroid Science* republish this case report for two reasons: First, many people have requested reprints of the original case report. To get reprints, these patients and clinicians had to contact my office. The reason is that the paper is no longer available online or in an accessible journal. In 1996, McDowell Publishing Company, LLC, who owned the journal that first published the report, sold the journal to Haworth Medical Press. The latter publisher, however, did not make available the journal issue that the case report had been published in. *Thyroid Science*'s open-access republishing of the paper now makes it perpetually available to anyone who finds its contents of interest.

My second reason for asking that *Thyroid Science* republish the report is the utter failure of fibromyalgia researchers in general to open their eyes to an obvious truth: that inadequate thyroid hormone regulation is the main underlying mechanisms of most patients so-called fibromyalgia. That I say that this is an obvious truth does not mean that all cases of fibromyalgia are easily solved simply by treating treating the patient with the proper form and dosage of thyroid hormone. As my colleague David Derry, MD, long ago pointed out in the British Journal of Medicine, living long years with untreated or undertreated hypothyroidism causes most patients to accrue secondary, tertiary, and other health complications that also must be disentangled from the enlarging clinical knot that further encumbers the patients. That a patient's fibromyaliga is long-standing usually means that successful recovery is a more complicated process.

Nonetheless, deductively formulated theory (the mathematical physicist's tool of victory that is absent from the intellectual armamentarium of the fibromyalgia establishment) shows unequivocally that the main underlying mechanism of fibromyalgia is too little thyroid hormone regulation. The inadequate thyroid hypothesis accounts for virtually *all* objective evidence we have on fibromyalgia. In stark contrast, no other hypothesis accounts for more than a minute fraction. Ignoring this fact forsakes fibromyalgia patients the world over, but it brings in a king's ransom from the purchase of ineffective and potentially harmful "fibromyalgia drugs" such as Lyrica and Cymbalta.

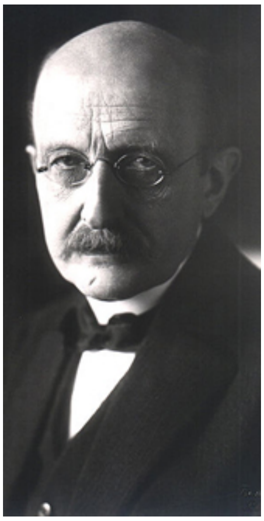
Why do fibromyalgia researchers in general ignore the obvious? Through more than two decades of involvement in this field, I have learned a list of disreputable reasons:

prejudice against the possibility of a causative thyroid connection, ignorance of basic and clinical thyroidology, egotistical pursuit of failed pet theories, and corruption through acceptance of judgment-forming grants and other perks from Big Pharma to develop drugs for fibromyalgia that are palliative at best and harmful at worst.

Despite many prominent fibromyalgia researchers claiming to be pursuing the underlying mechanism(s) of what we call fibromyalgia, they look everywhere but in the right direction. But while the researchers have spent decades looking in all the wrong directions, countless fibromyalgia patients—such as the female I describe in the case report—have recovered full health by the intelligent use of thyroid hormone as part of a comprehensive program of metabolic rehabilitation. Many have accomplished this by taking their health care into their own hands, while others have had the help of enlightened and collaborative clinicians.

My friend and colleague Richard L. Garrison, MD, for example, with T3 therapy and other assertive thyroid therapies, helped countless fibromyalgia patients to recover their health. This infuriated jealous physicians who had gaven the patients quack diagnoses of psychiatric disorders. Dr. Garrison was brutally punished for his crime of being scientific, humanitarian, and effective with patients. But emails I still receive some 3 years after his death tell me that for every physician who detested his clinical successes with fibromyalgia patients is at least matched by recovered patients who still adore him for enabling them to recover their health.

I republish this 1995 report with sorrow in my heart over the persecution of courageous physicians such as Dr. Richard L. Garrison who relieved so many patients suffering with the intelligent use of thyroid hormone. My sorrow is even deeper, however, over the millions of fibromyalgia patients who today are improperly treated for profit with Big Pharma's drugs. As my colleagues and I showed many years ago (and typified by the case we republish today in *Thyroid Science)*, the continued suffering of most of those people is avoidable. But sadly, we now live in a world where drug companies and researchers they fund steadily more make their fortunes from sustaining the suffering of other human beings.



Max Planck, PhD
Circa 1947

I find it more than difficult at times to live with the awareness that millions of fibromyalgia patients spend their lives suffering needlessly. But I find some solace in a famous statement by physicist Max Planck, the founder of quantum theory: *"A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it."*

And happily, a new generation appears to me to be sprouting in the field of fibromyalgia. At this time, Ian R. Carroll, MD at Stanford University School of Medicine is conducting a study of T3 for fibromyalgia patients. The title of his study is, "T3 for Fibromyalgia: a Pilot Double-blind Non-randomized Clinical Trial." I have no idea yet how this study will unfold. No research team I am aware other than mine has extensive research and clinical experience in treating fibromyalgia patients effectively with T3. But Dr. Carroll was unaware of my research team and our work until recently, when I learned of his study and sent him a copy of my book *The Metabolic Treatment of Fibromyalgia*. As his pilot study nears its end, he and I have just begun to correspond.

With no intent of malice, but only the hope of seeing the relief of untold and unnecessary human suffering, I am impatient for the passing of that generation of closed-minded fibromyalgia researchers. Before much more time passes, I hope to see a new and enlightened generation of researchers and clinicians that declines to assign the label "fibromyalgia" to people with chronic widespread pain and simply treats them effectively for their hypothyroidism or thyroid hormone resistance. In the mean time, if the case we republish today leads to even one patient's pain relief tomorrow, I will pleased indeed that I wrote the report fifteen years ago.

John C Lowe

Original Abstract. The main purpose of this case report is to illustrate a clinical observation common to me: that fibromyalgia patients with central hypothyroidism who fail to benefit from T4 or desiccated thyroid completely recover when they switch to T3. Changing status in the patient was evaluated in three ways: a psychiatrist used a depression inventory, a physical therapist performed functional musculoskeletal assessments, and I performed algometer tender point exams and monitored symptoms. I hope the description of the management of this case provides a protocol that other clinicians will use with fibromyalgia patients similar to the one who is the subject of this report.

Key Words. Algometry • Desiccated thyroid • Fibromyalgia • Hypothyroidism • T3 • T4 • TSH

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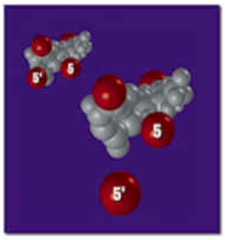

Drawing from the cover of Dr. Lowe's book *The Metabolic Treatment of Fibromyalgia* (E-chapters available)

First 16 Years of drlowe.com

Dr. John C. Lowe
March 20, 2011

January, 2011 marked the 16-year anniversary of drlowe.com. I initially had a definite vision of what drlowe.com was to be, and I still maintain that vision: that is, the website is to be an abundant source of information solidly based on science and logic and of practical value to patients and clinicians who deal with hypothyroidism, thyroid hormone resistance, and fibromyalgia.

I learned early during the last 16 years that the endocrinology specialty's judgment is corrupted by financial inducements from drug companies that profit from the TSH test and T4 replacement. All those years ago, my intention was to help revise the often harmful standard of care imposed by the endocrinology specialty for commercial rather than scientific reasons.

After careful consideration in the last several years, however, I realized that the specialty has its heels dug in; it's clear to me that the specialty won't volitionally rehabilitate itself into a rational, scientific, ethical, and respectable medical specialty.

Rather than rehabilitate, to this day, the specialty practices thuggery on a par with that of traditional organized crime. It does so by intimidating and persecuting clinicians who fail to cooperate in restricting their patients to T4 replacement—an often ineffective and harmful approach to therapy that's hugely profitable to Big Pharma and, by *quid pro quo*, to the specialty itself.

The well-intending persecuted clinicians are guilty of recognizing that T4 replacement doesn't work for and harms many patients. And they are guilty of having the courage to abide by the Hippocratic oath in using thyroid hormone therapies that get their patients well.

The thuggery of the specialty is in highly active gear. We know this because regularly, clinicians contact us and tell us of actions being taken against them by medical regulatory boards. Invariably, the action involves testimony against the clinicians by members of the endocrinology specialty or affiliates of theirs.

And what is the ultimate consequence of these actions against so many well-intended clinicians? Patients who need safe and effective thyroid hormone therapy are restricted to T4 replacement—an approach that published studies clearly show to be ineffective and harmful for many patients.

It seems that most every community has members of the endocrinology specialty who function as thugs. They act as enforcers of the command that clinicians use *only* TSH testing and T4 products. These thug endocrinologists file complaints against noncompliant clinicians. Then they testify against the clinicians before regulatory boards and courts and walk away scot-free after giving scientifically-false testimony in courts of law and other legal venues.

Experience tells me that the endocrinology specialty won't relent—not until it's forced to do so, probably by class action law suits and by forcible complaints for violations of medical ethics to purveyors of medical regulatory boards. To me, the final solution lies in the education of patients, clinicians, and legislators; legislation to disempower the endocrinology specialty from further harm to patients, clinicians, and the public welfare; and litigation against the specialty and its corporation supporters.

The force of unforgiving corruption by the specialty and its affiliates has long loomed over me and my medical colleagues. Because of this, at the beginning of 2010, I decided to preemptively remove from my back the target known as "licensed clinician." Having divested myself of that particular easy target, I'm now free to communicate with people (patients, their loved ones, and their clinicians) simply as a clinical researcher, educator, and natural health advocate.

Now, rather than clinical work with patients, we do educational and informational consulting with clinicians and clients. And we're especially dedicated to help a special group of countless thousands: those who—knowing that the endocrinology specialty has forsaken them to share power and profit with Big Pharma—have taken their health and welfare into their own hands and now self treat.

| *A personal appeal to our readers*:
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Dr. John C. Lowe

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Newsletters. A large amount of free information is contained within the webpages of drlowe.com. We'll continue to add to that free information.

I often come across information that I believe will be of value to many of our thousands of readers. Sometimes the information is new, and sometimes it's so old that it's been forgotten despite it's usefulness. We sometimes put the information on a webpage and list it in the Latest Updates. (We've included Latest Update links in the drop down menus for "Home & Contacts" and "Q&As & Newsletters.")

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Franconia Ltd began publishing *Thyroid Science* in 2005. At the time, I envisioned the journal as a forum where natural medicine or alternative clinicians and researchers would publish their papers. I wanted this because, I'm convinced, the traditional endocrinology journals are largely propaganda tools for the pharmaceutical companies that have corrupted the endocrinology specialty. Those journals censor submitted papers that might not be favorable to the financial interests of the drug companies that advertise in them.

As the years have past, I learned that only a few natural medicine or alternative clinicians, especially courageous ones, are willing to publish their views in *Thyroid Science.* Many have been frank in telling me that they cannot risk coming to the attention of thug endocrinologists in their

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to control and enhance their own health to succeed at that promising venture. Most patients don't need licensed clinicians, as the lab tests, nutraceuticals, and medications they need are available without prescriptions. And unfettered by licensing restrictions, I'm free, as a peer, to share these sources with our consulting clients.

Our main purpose, then, is to help you optimize your health through providing you with rationally- and scientifically-derived information. We support you in using this information whether or not you choose to use the help of licensed clinicians. Regardless of your choice, we'll be grateful if you'll help by sending us feedback on how we can better serve this purpose. All best wishes,

John C. Lowe

patients' T4 doses are adjusted according to their TSH levels.

At the same time, researchers from many medical specialties across the globe publish in *Thyroid Science.* These researchers and clinicians include many endocrinologists. As a result, we've changed the major aim of the journal. We still publish papers from natural medicine and alternative clinicians and researchers. But our main aim now includes taking the opportunity to communicate with endocrinologists and other specialists who practice according to the specialty's dictates.

The special purpose of our communication with those specialists is to let them know that there are numerous scientifically-based approaches to thyroid hormone therapy in addition to T4 replacement. We also let them know of scientific evidence that T4 replacement is for many patients clinically inferior and harmful.

So far, those who've published in *Thyroid Science* have been open to hearing this information, which they were unaware of before. In this sense, I see the journal as a Trojan Horse exerting a positive influence within the walls of mainstream medicine, including the endocrinology specialty.

• **ThyroidScience.us Update**: In this newsletter, we provide information we consider useful for those interested in Franconia Ltd's nutraceuticals, such as Thyro-Gold. The website is www.ThyroidScience.us. However, we often instead include this information in *Dr. John C. Lowe's Newsletter.*

• **Fibromyalgia Research Foundation Newsletter**. The main underlying mechanism of what we call "fibromyalgia" is now *long known*. The main mechanism is too little thyroid hormone regulation of cell function. Of course, old-guard rheumatology fibromyalgia researchers appear completely bereft of any awareness of this fact. Because of this, we only occasionally send newsletters from the foundation's website, www.FibromyalgiaResearch.org. But when we do, the information is important for those who've received the diagnosis of fibromyalgia.

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Adrenal Fatigue—A Real Disorder No Matter What its Name: A Response to Dr. Peter Hibberd

Dr. John C. Lowe

Yesterday afternoon, I was working to finish a newsletter that contained an article I've written on thyroid antibodies. I knew that many of our readers would find the topic interesting and helpful. But then something happened that abruptly stopped the press. A friend sent me a copy of Dr. Peter Hibberd's latest newsletter.

Hibberd's newsletter contains an inquiry from someone named Jim Z: "Please explain," Jim asks Dr. Hibberd, "what causes adrenal fatigue, how to treat it, and how long it takes to recover." When I read Dr. Hibberd's answer, I put away the antibody article and wrote this response to his answer to Jim. Below, I address each part of Hibberd's one paragraph answer.

Terms Physicians Use. In answering Jim, Dr. Hibberd first wrote, "Adrenal fatigue is not a term physicians use." This statement is less important than the others Hibberd made, but as it is categorically false, it needs correcting.

Dr. James Wilson, author of *Adrenal Fatigue*,[7] is a PhD, and he's also a chiropractic and naturopathic physician. If no other physician in the world uses the term adrenal fatigue, Dr. Wilson certainly does, and that fact alone refutes Hibberd's absolutistic pronouncement. Hibberd, of course, may not consider chiropractic and naturopathic doctors physicians. (Labs and insurance companies classify them as physicians, and many states in the U.S. license them as such. But this is a quibble, so I'll move on.)

Even if Hibberd doesn't consider Dr. Wilson a physician, Hibberd's statement is still patently false. I've attended lectures by Dr. Wilson on adrenal fatigue in which he addressed audiences of up to 700 clinicians; most of them were MDs and DOs. Also, Dr. Wilson often lectures across the nation to other groups of physicians. And he isn't the only physician who teaches other physicians to diagnose and treat adrenal fatigue. The total number of physicians who have studied under Dr. Wilson and other believers-in-adrenal-fatigue is assuredly large, and I'm confident that most of them do use the term adrenal fatigue. I've personally talked with scores of physicians specifically about the disorder, and we all have conversed using the term Dr. Hibberd denies physicians use.

Many conventional physicians, including endocrinologists, often discuss health problems related to low levels of cortisol. It's true that when they do, most use older terms such as "hypoadrenalism," "adrenal hypofunction," and most often, "adrenal insufficiency." These terms, of course, are only synonyms for the newer term, "adrenal fatigue." But as you'll see, Dr. Hibberd even questions the existence of what conventional physicians call adrenal insufficiency.

Symptoms from Low Cortisol. Dr. Hibberd went on to say to Jim, "It [adrenal fatigue] is popular with alternative medical publications and is used to describe vague symptoms of fatigue, irritability, and body aches *allegedly* arising from adrenal insufficiency." (Italics mine.)

Here, Hibberd appears to question that such symptoms arise from adrenal insufficiency. I say this because he refers to the association between the symptoms and adrenal insufficiency as alleged. This means, of course, that alternative clinicians assert the association between the symptoms and the disorder with no proof of it.

Some clinicians do use the term adrenal fatigue to refer to patterns of symptoms. I certainly do. I do so because it's well documented that patients with too little adrenal production of cortisol experience the symptoms. Descriptions of the symptoms extend back at least 100 years in medical textbooks. Today, one can quickly find descriptions of the same symptoms through search engines on the Internet and at PubMed. Hibberd can also go to any medical library, and there, he'll find scores of recent textbooks on diagnosis that describe these same symptoms "arising from 'adrenal insufficiency.'" Many such books describe the symptoms of different degrees of adrenal insufficiency. They describe the symptoms of severe adrenal insufficiency including the potentially-deadly shock of adrenal crisis. But they also describe milder symptoms from less severe cortisol deficiencies. After *Taber's Medical Dictionary*,[5,p.40] we can refer to the latter as "relative" adrenal insufficiency, meaning relative to reference-range levels of cortisol.

As any other physician does, Dr. Hibberd needs to learn the symptoms of adrenal fatigue, adrenal insufficiency, or whatever one prefers to call it. He can do so within less than five minutes by Googling the two terms "adrenal insufficiency and symptoms." A huge number of medically-related websites will come up. When I did this a few minutes ago, Google gave me a count of sites that contain the two terms. The number was 251,000. When I typed in "symptoms and adrenal fatigue," Google indicated that 218,000 websites contain the terms.

When I used "adrenal fatigue" as the search term in PubMed, 919 abstracts of published papers came up. And when I used "adrenal insufficiency" as the search term, the number of abstracts that came up was 11,980. That's a lot of publications about a medical disorder that supposedly doesn't exist. Hundreds of the papers indexed in PubMed—far too many to reference here—*resoundingly* refute Hibberd's claim that ". . . tests used to define a decrease in adrenal function known [*sic*] do not support the existence of the condition.

The first paper indexed by PubMed that mentions adrenal insufficiency is dated 1922. It was published in the *Journal of Physiology*.[14] Its title is, "On the concentration of the blood and the effects of histamine in adrenal insufficiency." Hibberd implies that the term adrenal insufficiency is used only in "alternative medicine publications." The *Journal of Physiology*, however, is not an alternative medicine publication. Nor are scores of other journals that have published hundreds of papers on the condition Hibberd calls "allegedly" adrenal insufficiency. Consider one, the French medical journal *La Presse Medicale*. In 1953, it published a paper[6] about a symptom Hibberd seems to doubt can result from adrenal fatigue. The paper's title is, "Fatigue; a functional adrenal insufficiency syndrome." Hibberd can easily confirm that *La Presse Medicale* is far from an alternative publication; it's about as conventional as medical journals get.

Learning through Personal Experience. For some physicians, published scientific evidence is not good enough. They believe only what they themselves personally experience. If this is true for Dr. Hibberd, I suggest that he test through personal experience whether or not symptoms result from adrenal insufficiency. He can do this by undergoing a modified metyrapone test.

Metyrapone has long been used by endocrinologists to diagnose the adrenal condition that Hibberd denies exists. Diagnosticians even use the drug to differentiate between two well-known forms of adrenal insufficiency.[3][4] The drug lowers cortisol levels by preventing the last step in the production of cortisol. It does so by blocking the enzyme 11beta-hydroxylase that triggers the conversion of 11-deoxycortisol to cortisol.[4,pp.278-9]

I challenge Dr. Hibberd to use metyrapone to lower his cortisol level by, say, 40%, and keep it there for a week while he works the most demanding hours in the ER. If he then comes back and tells us with a straight face that symptoms such as fatigue don't develop from low cortisol levels (as in adrenal fatigue), I may start to doubt my own sanity. Instead, though, I'm confident that he'll come back a physician newly enlightened about the fact of adrenal fatigue.

But taking the drug metyrapone isn't the only way to induce adrenal insufficiency. Stress can also do it, as Dr. Wilson explains so well.[7] In fact, stress is basic to the concept of adrenal fatigue. Studies have shown that patients who have had chronic stress, sometimes resulting in post-traumatic-stress-disorder, have low urinary and blood cortisol levels.[8][9] In one study, the more combat experience veterans had, the lower their blood levels of cortisol.[10] Researchers found that women with chronic pelvic pain had lower blood and saliva levels of cortisol. The researchers conjectured that the women's pain resulted from too little protective cortisol. They reported that the women's low cortisol was associated with more abusive experiences and a higher number of "major life events."[11] And low cortisol levels have followed the stress of recent myocardial infarctions.[12]

Conclusions. Dr. Hibberd concluded: "Be careful accepting diagnostic labels from an unqualified individual. Instead, consult your personal physician for [*sic*] correct diagnosis. Your recovery time will depend upon treatment options provided once your real diagnosis has been established."

When it comes to diagnosing and treating the well-documented disorder of adrenal insufficiency, who is the "unqualified individual" (to use Hibberd's term)? In my opinion, one such person is the clinician who is unaware that the disorder exists. This clinician is not likely to order tests that can verify that the disorder is the cause of a patient's symptoms. In that case, the patient's "recovery time" (to use another of Hibberd's terms) will be delayed until he finds another clinician who'll accurately diagnose the disorder and properly treat the patient for it.

Unfortunately, the delay can compound the patient's woes. Consider, for example, the patient with antibodies against the cortex of his adrenal glands. These can cause the form of adrenal insufficiency called "Addison's disease." Classic symptoms of the disorder are weakness and fatigue that clinicians used to call "asthenia." The antibodies lower cortisol levels by destroying an enzyme, 12-hydroxylase, that converts a form of progesterone to cortisol. If a physician is aware that low cortisol could be the cause of his patient's fatigue, he's likely to order appropriate tests. These can confirm both the low cortisol and the autoimmune process. With proper treatment, the cost to the patient's health can be limited to the fatigue he suffered before proper treatment began.

But consider what can happen if the physician falsely believes that low cortisol from adrenal insufficiency doesn't occur and doesn't cause fatigue. He may fail to confirm through testing the cause of the patient's fatigue. Then, as precious time passes, the inflammatory process in the patient's adrenal glands may progress, and he may end up with widespread destruction of the cortex of the glands. This will result in deficiencies of other hormones in addition to cortisol.[13] In this happens, the cost to the patient's health will *far* exceed his experience of fatigue.

To believe that adrenal insufficiency doesn't exist is about like believing there is no such condition called anemia. The fact is, Dr. Hibberd is as likely to encounter patients with adrenal fatigue as he is those with anemia. I trust that he wants to serve all his patients well. So that he can—including those with adrenal fatigue—I urge him to correct his false beliefs about the disorder (even if he refuses to call it by the new term), and to learn how to diagnose and treat it so he can help those countless people whose symptoms are caused by it.

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Tammy Lowe

If you want to discuss the services we provide, please contact me. You can reach me by email at Tammy@drlowe.com or by phone at 603-391-6061.

Dr. John C. Lowe, PLLC
Tel (603) 391-6061 Fax (303) 496-6200 Tammy@drlowe.com

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Archived Newsletters

Air Hunger to Death: Breathing Problems of Hypothyroid Patients

Dr. John C. Lowe
February 25, 2005 (Updated January 30, 2006)
Send Comments & Questions to
drlowe@drlowe.com

Last week I consulted long distance with a young hypothyroid woman who had a distressing symptom—trouble getting a deep enough breath. She told me, "I just can't seem to get in enough air." She said her doctor doesn't believe her hypothyroidism is the cause of her breathing problem.

I referred the patient to several sections of my book, *The Metabolic Treatment of Fibromyalgia*.[1] In those sections, I explain that labored breathing is a troubling symptom for which some hypothyroid patients seek medical care.[2, 11-13, 15-24] Medical journals contain many reports of some patients with hypothyroidism or thyroid hormone resistance having labored breathing. The difficult breathing is called "air hunger" or "dyspnea." Air hunger, however, isn't the worst of the breathing troubles of some patients with too little thyroid hormone regulation.

In *The Metabolic Treatment of Fibromyalgia*,[1] I explain various mechanisms of these patients' air hunger, all of which result from too little thyroid hormone regulation. One mechanism is weakness of their respiratory muscles, including the diaphragm.[22-23] Researchers call this weakness of respiratory muscles "hypothyroid myopathy."

Another mechanism is impairment of the phrenic nerves that regulate contractions of the diaphragm. When impaired, these nerves send too few signals to the diaphragm for it to contract normally.[23]

A third mechanism is decreased "central drive of respiration."[34] This means that the brain centers that regulate breathing are impaired by too little thyroid hormone regulation.

Still another mechanism is abnormal heart and lung function.[14-15,20] Some patients suffer from air hunger only when they exert themselves; others do so even at rest.

The young hypothyroid woman I consulted with had been on T4-replacement for three months. She had been troubled with hypothyroid symptoms, including air hunger, for a year before her doctor diagnosed her hypothyroidism. The T4-replacement had slightly improved her fatigue and dry skin, but not her air hunger. Her dose of T4 was 100 mcg (0.1 mg) per day.

I was not surprised that this patient was still suffering from hypothyroid symptoms, including air hunger. To illustrate, consider the study data reported by a group of endocrinologists in 1997.[30] They measured nine hypothyroid patients' TSH levels and their resting metabolic rates, and compared them to their doses of T4. I analyzed their data from a perspective different from theirs.

At one point in the study, six of the endocrinologists' nine patients were using 100 mcg (0.1 mg) of T4. For three of these patients, this dose provided normal metabolic rates, although the rates of two of them were low normal. These two patients' metabolic rates were 7% and 9% below the calculated average rate. (We consider a rate abnormally low only if it's 10% or more below the calculated average rate). For the other three patients on 100 mcg of T4, the dose was woefully inadequate: One patient's metabolic rate was 18% below normal, another's was 23% below, and a third patient's was 26% below normal.

The endocrinologists didn't report this finding. I found it simply by looking at their data from a different perspective. From this vantage point, their own data show that some hypothyroid patients are kept hypometabolic on 100 mcg of T4. We find this regularly in our clinic when we measure the metabolic rates of patients on T4-replacement. And 100 mcg of T4 is obviously not working for this young woman, whose main troubling symptom is air hunger.

Doctor-Caused Lifelong Breathing Problem. Yesterday I consulted long distance with a woman in her seventies who has had breathing troubles far worse than those of the young woman I mentioned above. In the early 1970s—before the *Tyranny of the TSH*[32] began—an endocrinologist treated her for hypothyroidism. Through trial-and-error, he found that her safe and effective dose of Armour Thyroid was 6 grains (360 mg).

She remained well on that dose until, years later, a second endocrinologist found her TSH level suppressed. The patient had no symptoms of overstimulation. Despite that, this endocrinologist

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Continued from bottom of left column . . .

Hypothyroidism and Obstructive Sleep Apnea. Hudgel recommended thyroid hormone as a "ventilatory stimulant" for hypothyroid patients with sleep-disordered breathing.[5] He explained that in 1964, Massumi and Winnacker reported the association of sleep-disordered breathing with hypothyroidism.[6] Their report was about two hypothyroid patients who had obstructive sleep apnea. In 1981, Orr reported the results of polysomnograms (recordings of physiology during sleep) of three hypothyroid patients.[7] The tests showed repetitive obstructive apneas during sleep. Further testing by Rajagopal tightly linked hypothyroidism to obstructive sleep apnea.[8] Nine of his 11 consecutive hypothyroid patients had apnea.

Not all hypothyroid patients, of course, have obstructive sleep apnea. Lin found that among 25 hypothyroid patients, only 25% had sleep apnea.[9] The patients who had apnea were older and more obese than the patients without apnea. And not all patients with obstructive sleep apnea are hypothyroid. Lin found that only 3% of patients with apnea were hypothyroid.[9]

But for most hypothyroid patients who do have sleep apnea, the consequences can be troubling.[10] For example, because they don't sleep deeply long enough, they can be severely fatigued throughout the day. And as the section below shows, for at least one hypothyroid patient, apnea wasn't just troubling; it was fatal.

First Reported Death From Hypothyroidism and Sleep Apnea. In 1999, doctors reported the first case of a hypothyroid patient who suddenly died from sleep apnea.[4] The patient was a 48-year-old man who was short and slightly overweight. He had never been treated for his hypothyroidism.

For several years, the patient suffered from air hunger at night. In the previous few weeks, his air hunger had worsened. In the hospital, doctors noted that he was lucid, but his mental and physical functions were slow. They found that he had a multinodular goiter that had moved his windpipe (trachea) from its normal position. His tongue was enlarged, and his pharynx (the cavity that connects the mouth and nasal passages to the esophagus) was swollen with edema. His blood was adequately saturated with oxygen at 97%.

Doctors treated the man with T3 and hydrocortisone. They doubted that he had sleep apnea syndrome, but they applied pulse oximetry. (Pulse oximetry is a monitor, usually with a finger sensor, used during anesthesia and critical care. It measures oxygen saturation of arterial blood.) The man suddenly died seven hours later.

The oximetry record showed that over the seven-hour period, the patient had prolonged episodes of sleep apnea. These episodes had caused deep drops in oxygen saturation of his blood. The doctors who reported the man's death urged other doctors to promptly diagnose hypothyroidism that's associated with obstructive sleep apnea. They noted that the condition can become serious and require intensive care with continuous nasal airway positive pressure. They wrote that some patients may need tracheal intubation with assisted ventilation. They cautioned, "Continuous cardiac monitoring should also be carried out, given the risk for acute coronary complications and ventricular arrhythmias in the early phases of substitutive therapy with thyroid hormone."

Conclusion: The studies I've cited in this report show that too little thyroid hormone regulation can cause a variety of breathing problems. These range from mere frustrating air hunger to death from sleep apnea. If you have a breathing problem and your doctor can't find the cause, ask him or her to evaluate you for hypothyroidism or thyroid hormone resistance. If you're being treated for hypothyroidism with T4-replacement, ask your doctor to insisted that she reduce her dose of Amour. She complied, lowering it to 4.5 grains (270 mg).

"Soon," she told me, "I simply was not functional. I was gasping for air and coughing so bad that I felt like I was damaging my lungs." To breathe, she had to sit upright on a sofa without leaning her head back to rest. This went on for eight weeks.

When her daughter, a nurse, phoned the endocrinologist, he denied that the patient's breathing problem was related to her lower dose of Armour. He advised her to consult an ear, nose, and throat specialist. She saw a lung specialist instead, and he prescribed 40 mg of cortisone and an inhaler. The inhaler enabled her to get through her days. But even with the help of the inhaler, she couldn't walk up a short flight of stairs without gasping for air. Her voice was so badly affected that she could no longer sing, which she had always enjoyed. "I could only croak," she said.

In March of 2004, she located the original endocrinologist who had put her on 6 grains of Armour in the early 1970s. Her put her back on that dose. "It took me the rest of the year to get off the cortisone and get well," she told me. "Before the second endocrinologist lowered my Armour dose, I'd never had any asthma or other breathing problems. Now I'm left with a lifelong breathing problem." She's largely over the breathing problems that began on the lower dose, but she still has to use an inhaler one or two times each day.

I admire this woman's strength of character in wresting control of her health away from her doctors. Some of them have recently tried to persuade her to lower her dose again. "They simply don't listen when I tell them what happened to me on the lower dose. I feel that I'm up against a wall of idiocy," she said. "I don't have too many years left to fool around with their book theories, and I'm not going to let them kill me." The tragic fact is, of course, that many doctors today would sacrifice her health and, indeed, even her life. Like most fanatics, to these doctors *any* price the patient might pay is worth achieving their obsessive goal—keeping the patient's TSH "in range."

Asthma. Some inhalants patients use to relieve their asthmatic symptoms work by stimulating beta$_2$-adrenergic receptors in the bronchial tubes.[28] Stimulating the receptors dilates the tubes and constricts blood vessels in their lining, which dries mucous secretions. These effects of the inhalants relieve shortness of breath, coughing, and wheezing respiration.[25,p.207]

An alternative to using the inhalers is to increase the number of beta$_2$-adrenergic receptors in the bronchial tubes by taking an effective daily dose of thyroid hormone.[33] T3 is especially useful for this purpose.

In 1991, Egyptian researchers treated 23 asthmatic children with T3.[29] The children weren't hypothyroid. During the 30 days of treatment, they continued to use their usual anti-asthma drugs as needed, but they reduced their doses as low as they could.

The researchers wrote, "They [the children] all reported at the end of the 30 days an obvious subjective improvement of their asthmatic conditions with a decrease in the number of exacerbations. Seven patients stopped their usual anti-asthmatic medicines, being maintained on T3 only and 3 have decreased the amount of bronchodilators needed. A significant improvement of pulmonary function tests was noted in all patients."

According to the researchers, "All patients tolerated well the T3 regimen without any adverse effect." They concluded that T3 induced beneficial effects: T3 "proves to be a useful adjuvant to classic anti-asthma therapy, and may reduce the amount of bronchodilators needed."

Other researchers reported that patients with asthma became hypothyroid from using iodine-containing expectorants. After becoming hypothyroid, their asthma worsened. The worsening of the asthma was relieved, however, when the patients stopped using the expectorants and their thyroid function became normal again.[27]

Another group of researchers took hypothyroid children off thyroid hormone for a month. By the end of the month, the children's bronchial tubes became more reactive to antigens. (Heightened reactivity of the bronchial tubes to antigens, of course, is the basis of allergy-induced asthma.) The children then resumed their thyroid hormone therapy. Their bronchial tubes, however, remained more reactive to antigens for two more months. Finally, after twenty more days, their bronchial tubes became normally reactive to antigens.[26]

Respiratory Failure and Other Breathing Problems. In 2004, doctors described a 36-year-old male admitted to the hospital for progressive respiratory failure.[3] His chest X-ray and CT scan were normal, but he had a severely slow heart rate (bradycardia) and his cognitive function was slow. His TSH was over 150 microU/ml (in the US, the current upper limit for a "normal" TSH is 2.5 or 3.03, depending on which authority one consults). After the man began thyroid hormone treatment, his respiratory function steadily improved.

The doctors who reported this patient's case listed five other respiratory disorders common among hypothyroid patients: dysfunction of the diaphragm, poor respiration from low central nervous system drive, obstruction of the airways, pleural effusion, and sleep apnea. They advised doctors to evaluate patients with respiratory problems for hypothyroidism. Ask your doctor to also consider that this thyroid hormone therapy leaves almost 50% of patients suffering from chronic hypothyroid symptoms.[31] Ask your doctor to also consider that you may need to switch to a more effective therapy such as a T4/T3 combination product or T3 alone. At minimum, if your doctor isn't aware that too little thyroid hormone regulation can cause breathing problems, share this special report with him or her. The doctor may use the information not only to relieve your breathing problem, but to help other patients, too.

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Anesthesiologists reported the case of a 58-year old man who was severely hypothyroid. They wrote that his hypothyroidism was the cause of "ventilatory failure." They described his 3-to-4 breaths per minute after surgery as an "exceedingly low" respiratory rate. The volume of air he took in each minute was low. Despite his low oxygen intake overall, he developed "primary acute respiratory alkalosis" (carbon dioxide loss from hyperventilation) and associated "hypocarbia" (abnormally low carbon dioxide in arteries). The anesthesiologists cautioned that severely hypothyroid patients are at risk for adverse events around the time of surgery. They are more sensitive to anesthetics, have a higher incidence of surgery-related cardiovascular disease, and have an increased risk for ventilatory failure following surgery.[34]

Hypothyroidism doesn't have to be severe to lead to weak breathing responses to increased carbon dioxide in the body. Researchers published a report on ten patients with hypothyroidism less severe than that of the patient in the above paragraph. Two of these patients had "blunted ventilatory responses to hypercapnea." This means that high carbon dioxide levels didn't provoke a normal increase in breathing to lower the carbon dioxide levels. The patients' breathing responses to increased carbon dioxide improved when they underwent thyroid hormone therapy.[35]

Continued at top of the right column . . .

Tammy@drlowe.com

Our Educational Consulting Service

We provide educational consulting to both patients and clinicians. Phone us at 603-391-6061, or preferably, write to us at Tammy@drlowe.com. Our fax number is 303-496-6200. ***—Tammy Lowe***

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The Metabolic Treatment of Fibromyalgia
by Dr. John C. Lowe
E-Chapters: Separate book chapters as pdfs

Dr. Lowe revises and updates his chapter on fibromyalgia for the *4th Edition* of the authoritative *Textbook of Natural Medicine.* The two-volume textbook is edited by Joseph Pizzorno, ND and Michael Murray, ND, and published by Elsevier.

"I finished the updating and revisions at 1 AM on October 12, 2011. This was after four days locked away in a motel where I often go to write for total concentration. While exhausting, few things in life are more exhilarating than to finish such a huge and precise writing task."

John C Lowe

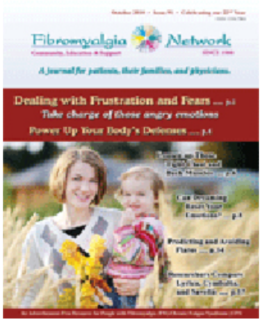
Interviews, Conversations, Talks, & Publications

Dr. Joseph Mercola & Dr. John C. Lowe discuss thyroid issues.
Dec. 31, 2010

Dec. 14, 2010. **Bette Dowdell & Dr. Lowe**:
Live Tele-seminar on "Dr. Lowe's Personal Thyroid Story."

(Click "Reply" to listen, or download the recording by clicking on "Right-Click to Download MP3")

Kristin Thorson's Magazine Interview in *Fibromyalgia Network*


Fibromyalgia Network
A journal for patients, their families, and physicians.
Dealing with Frustration and Fears ... p.1
Take charge of these angry emotions
Power Up Your Body's Defenses ... p.4

For more than 20 years, I've known of a person who has diligently worked for the well-being of fibromyalgia patients. She is Kristin Thorson, originally educated as a chemical engineer. Her work on behalf of fibromyalgia patients has been truly extraordinary.

Among Kristin's exceptional contributions to the cause of fibromyalgia patients has been her arranging for the financial funding of many fibromyalgia studies. Without the funding she arranged, we would be bereft of some of the information that has enabled us to better understand the nature of fibromyalgia. I'm personally grateful for her exceptional humanitarian work on behalf of fibromyalgia patients.

Kristin's organization is the Fibromyalgia Network. I encourage you to visit the Network's website and subscribe to their *Fibromyalgia Network* magazine (see the cover above).

Kristin contacted me last week, prompted in part by a study report conducted by a rheumatologist in Italy, Dr. Bazzichi. I hadn't heard of the report and I'm grateful to Kristin for bringing it to my attention.

The title of Dr. Bazzichi's report makes clear the implications of her study findings: "Thyroid autoimmunity may represent a predisposition for the development of fibromyalgia?"[1] (I'll soon provide details of the study and its results.)

In 2005, Kristin wrote an article in the *Fibromyalgia Network* magazine about metabolism and fibromyalgia. She is now writing another article on that topic. Her focus is the research findings of Dr. Bazzichi and my research teams' work on the thyroid-related bases of fibromyalgia. Kristin and I spent some four hours on the telephone discussing the topic while she conducted an interview.

We will send out notice of when Kristin's article will be published in the *Fibromyalgia Network* magazine. I'm immensely grateful to Kristin for giving the thyroid line of research due attention after so many years of censorship by others.

Kristin Thorson
Fibromyalgia Network
www.fmnetnews.com
7371 E Tanque Verde Rd
Tucson, AZ 85749
TEL: (800) 853-2929
FAX: (520) 290-5550

To receive a copy of the issue containing the article, please contact Fibromyalgia Network:
Fibromyalgia Network, P.O. Box 31750, Tucson, AZ 85751 *(800) 853-2929*.

Reference

1. Bazzichi, L., Rossi, A., Zirafa, C., et al.: Thyroid autoimmunity may represent a predisposition for the development of fibromyalgia? *Rheumatology Int.*, 2010, Nov 18.

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The Metabolic Treatment of Fibromyalgia
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Menu of Q&A Topics

4/14/11	If I stockpile dietary desiccated thyroid to use in the future, how long does it keep its potency?
4/7/11	Interview of Dr. Lowe on fibromyalgia by Dr. Leisa Wheeler, Tuesday, March 4th, 2008 **YouTube**
3/22/11	Why are my free T4 and free T3 much *lower* instead of high after starting to take Armour Thyroid?
3/16/11	Nuclear plant meltdowns: Is potassium iodide protection enough? Special newsletter by Dr. Lowe
2/26/11	Interview with Dr. Lowe by Dr. Joseph Mercola: at drlowe.com
2/26/11	Interview with Dr. Lowe by Dr. Joseph Mercola: at Mercola.com
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1/29/11	Where to buy inexpensive quality nutritional supplments Tammy Lowe
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12/14/10	Dr. Lowe's fibromyalgia chapter for 4th edition of *Textbook of Natural Medicine: updated and revised*
12/14/10	Kristin Thorsen magazine (*Fibromyalgia Network*) interview with Dr. Lowe
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9/14/10	Listen (free) to my hour talk with dynamic & witty Bette Dowdell of "Too Pooped to Participate"
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6/21/10	Is there any way to tell whether thyroid hormone is getting to my cells?
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3/31/10	Concern about selenium poisoning from HSF: The most common email we receive
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3/8/10	In-range TSH but high anti-thyroid antibodies: Women at risk for infertility & trouble pregnancies.
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2/1/10	Is there any benefit to using Thyro-Gold in addition to other thyroid hormone products? Dr. Lowe
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News from Dr. John C. Lowe

Metabolic Research and Educational Consulting — *April 17, 2010*
The Metabolic Treatment of Fibromyalgia by Dr. Lowe

drlowe.com/contactus.htm (603) 391-6061 Tammy@drlowe.com
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If You Still Eat Non-Organic U.S. Beef . . .

Why Thyro-Gold Contains Free-Range New Zealand Beef

I've known for a long time that US regulatory agencies neglect to protect American beef consumers from potential harm from US beef.

The potential adverse effects can be severe. Tony Corbo of the consumer advocacy group Food and Water Watch commented on a recent report by the Inspector General of the US Department of Agriculture. Corbo said, "Some of the residues that the Inspector General cited [as not being monitored] could be carcinogenic, as they accumulate over a period of time in the body." In commenting about some contaminants not tested for in US beef, Corbo added, "Over time, as they accumulate in body, they can affect organs . . . they can cause organic failure . . . ."

I haven't eaten non-organic U.S. beef for decades, and knowing what I know about it, I probably never will eat it again. On occasion I do eat beef, but it's *always* certified organic. I urge my loved ones never to eat non-organic US beef. To my horror, though, most of my pleadings are to no avail.

I want to briefly explain my adversity to non-organic US beef. At the same time, I'll explain why the Thyro-Gold (the new dietary desiccated thyroid products that I formulated) contains thyroid tissue from pristinely clean New Zealand beef.

U.S. Inspection Standards are Substandard. In 2008, Mexico turned away a shipment of U.S. beef because of its high and potentially toxic copper levels. The rejected beef, however, could still be sold to US consumers. The reason is that the US has no limit on how much copper can be in beef.

My reasons for boycotting US non-organic beef are more broad based than Mexico's, and with good reason. To understand my position, do Internet searchers for whistle-blowing scientists who've told the truth about Monsanto's genetically modified hormone called "rbST," which is given to US beef.

I encourage those who still eat non-organic US beef to listen to the current word of caution from the Inspector General of the US Department of Agriculture. His report states that US government standards are too lax or even nonexistent. The standards don't adequately guard against the contamination of meat by traces of heavy metals, antibiotics, and pesticides.

Non-organic U.S. cattle typically live fenced at "feed lots."

As Tony Corbo (Food and Water Watch) said, "The government has fallen down on the job here." CNN's Brad Todd reported the Inspector General's warning, and CNN provides a video of Brad's report on lax U.S. standards: http://edition.cnn.com/2010/US/04/14/us.beef.testing/index.html?hpt=T2

Thyro-Gold Intended as the Gold Standard for Dietary Desiccated Thyroid. After intensely studying Hypo Support Formula (HSF) for a good year-and-a-half, I came to believe the product has at least two potential problems. One of the potential problems is the amount of selenium in HSF capsules.

Because of the problems, I've worked with a formulating biochemist to develop an enhanced dietary desiccated thyroid product. The product is called Thyro-Gold. We picked that name because we intend for the product to be the gold standard for dietary desiccated thyroid. We've made sure Thyro-Gold is free from the potential problems I see with HSF. Thyro-Gold, a Franconia nutraceutical, will be available in a few weeks.

Organochlorines: Chemical Pollutants that Disrupt the Thyroid System *in Offspring*

Organochlorines (ôr' g∂ nō Khlôr' ēns) are compounds that contain carbon and chlorine. Our world has thousands of different compounds of organochlorine.

Some organochlorines occur naturally. For example, they occur in the hot areas around forest fires and volcanoes, where lightening has started fires, and during the decomposition of biological matter. Researchers have isolated them in marine algae and tree frogs.

Most organochlorines, however, are man made. They're produced as products of combustion, as in car engines, and chemists have tailor made them for industrial processes. As the New Zealand Ministry for the Environment wrote, ". . . the vast majority have been specifically manufactured for a wide range of uses, including pharmaceuticals, pesticides, plastics, and solvents."[1]

Pesticide residues on food are a major source of human organochlorine exposure.[5] Even the compounds that have been banned for decades are show up consistently in food samples tested by the U.S. FDA.[6]

Most of the compounds decompose and disperse through the environment. But some are stable chemicals that break down slowly. These remain in our environment for a long time. Research has shown that some are toxic to humans and other animals.

As the Ministry for the Environment notes, some organochlorines form vapor. Air currents carry the vapor for long distances. Eventually it condenses and deposits on land and water, especially in cold regions. "When organochlorines contaminate the food supply of animals, the organochlorines become more concentrated as they move up through the food chain. For this reason the highest levels of organochlorines are found in species at the top of the food chain: human beings, fish-eating birds and marine mammals. They build up in the fatty tissues and stay in the body for a long time because they are only slowly metabolised and excreted."[1]

The Ministry cites the four properties of organochlorines: they persist in the environment and in animals, many become vapor, they are toxic, and they're more concentrated as they move up the food chain. They are an international problem of serious concern.

Organochlorines as Thyroid and Glucose Disruptors. Researchers in Slovakia conducted a study of the effects of organochlorines on the thyroid and glucose-regulation systems in humans.[2]

The investigators studied young adults from an area heavily polluted with organochlorines. I'll call these people the "organochlorine group." The group consisted of 137 females and 94 males aged 21-to-35 years. (This group of people also had "strikingly" high levels of other contaminants called PCBs, DDE, and HCB.)

The researchers compared the organochlorine group with another group of young adults. This second group consisted of 116 females and 107 males. They lived in another geographic area, one polluted with PCBs, DDE, HCB, and far less organochlorines than in the area where the organochlorine group lived. I'll call these people the "background-pollution group."

Compared to the background group, the organochlorine group had a significantly higher incidence of four abnormalities: enlarged thyroid glands, a higher incidence of thyroid-peroxidase antibodies, more prevalent TSH-receptor antibodies, and impaired fasting glucose regulation.

The researchers compared the pollution levels of the two groups of young adults to their parents. The parents lived in the two respective areas and were aged 41-to-55 years. Despite the lower level of organochlorines in people of the background group, they had about the same incidence of the abnormalities as their parents.

Because the background group had about the same incidence of abnormalities as all the parents, the investigators made another comparison. They measured the level of PCB pollution in all young adults in the background group. Then they selected for comparison members of the organochlorine groups who had nearly the same level of PCB pollution. Young adults in both groups had lower levels of the pollutants called DDE and HCB. However, despite roughly the same PCB, DDE, and HCB levels in the two groups, those in the organochlorine group had significantly higher incidences of enlarged thyroid glands, thyroid-peroxidase antibodies, TSH-receptor antibodies, and impaired fasting glucose.

The researchers reasoned that because the organochlorine group was more polluted with the compound, the group had a higher incidence of the abnormalities. However, the similar incidence of the abnormalities between the parents and the background group means that the adverse effects in young adults from organochlorine exposure didn't result from their actual body levels of the compounds, which were lower than in the organochlorine group. Instead, the abnormalities probably had another cause: exposure of their mothers to high levels of organochlorines during the young adults prenatal and perinatal life, that is, during gestation, especially after the 28th day.

The investigators thus noted that their findings are consistent with a recent view of other organochlorine researchers: that *organochlorines are endocrine disruptors that cause thyroid and glucose abnormalities that are transmitted from generation-to-generation*. In the case of their study subjects, the likely transmission was from pregnant mothers to offspring.

Avoiding Organochlorines. Compared to a single dose of a particular

In formulating Thyro-Gold, we went the extra mile. We wanted to be sure people who use the product can feel confident that it's a safe and otherwise high-quality product. To this end, I'd like to note the response to the Inspector General's report by the US National Cattlemen's Beef Association. The Association stated that ". . . the US beef supply is extraordinarily safe *by any nation's standards*." (Italics mine.)

I beg to differ! As the Inspector General's report shows, the US government is simply lax in its inspection standards. For example, US inspectors test for traces of only one type of pesticide while cows are potentially exposed to dozens of pesticides from run off from nearby agricultural facilities. Also, as with copper, the US hasn't set limits for some heavy metals. Moreover, as the Inspector General noted, the US government also isn't fully guarding against contamination of beef by traces of antibiotics. And this means that US beef consumers are subjected to potential harm from all three contaminants—heavy metals, antibiotics, and pesticides.

Despite the Cattlemen Association's statement, some other countries have stricter inspection standards than the US. Among those countries, New Zealand distinguishes itself. Our research tells us that New Zealand beef is second to none in terms of animal quality and inspection standards. That is why we chose New Zealand bovine thyroid tissue for Thyro-Gold.

Thyro-Gold contains thyroid tissue from free-range, grass-grazing New Zealand cows

The thyroid powder in Thyro-Gold comes from free-range, pasture-fed New Zealand cows. New Zealand is a major dairy-producing country that has banned Monsanto's rbST,[1] which is now owned by Eli Lilly and Company. rbST stands for "recombinant bovine somatotropin." (Somatotropin is a synonym for growth hormone.) Natural somatotropin stimulates the growth of calves and lactation in adult cows. The industrial production of rbST is a genetic manipulation. Chemists insert the gene that codes for somatotropin into bacteria. The bacteria then produce the hormone in large quantities. The plentiful supply of rbST enables beef producers to artificially stimulate the growth and milk production of cows.

Some scientists don't believe rbST is safe. Some have become whistleblowers after being subjected to pressured tactics by administrative superiors to ignore compromised evaluation standards apparently intended to get rbST approved for use despite potentials risks to the public.[2] One scientist, Dr. Margaret Hayden, testified before a Canadian Senate Committee that her research files on rbST were stolen from a locked file cabinet. She also testified that she had been present at a meeting where representatives of Monsanto, the makers of rbST, had been present. The representatives offered Health Canada two million dollars if the drug was approved. Hayden was then suspended for five days from work, and seven scientists later testified that the suspension was retaliation for her testimony to the Senate Committee.

I won't cite the detailed evidence here that I believe shows the poor quality of US non-organic beef in the US. I believe the poor quality would have been reflected in that of Canada's beef had the Canadian government not banned hbST in 1999.[3,p.35] To be brief, I include here a paragraph from the article on the two scientists punished before the ban for going public with their concerns about the approval process for rbST in Canada:

> "Health Canada is having trouble keeping these issues behind closed doors. In April 1999 the European Union audited Canada's meat supply and revealed 'serious deficiencies'. It documented widespread use of cancer causing hormones, antibiotics, endocrine disrupters and other hormonally active substances, all of which are banned in Europe. Canada promised that it could provide the European market (but not Canadians) with chemical free beef. Health Canada officials tried to write the audit off as a 'trade dispute' but these were the same substances that department scientists had recommended against approving"[2]

By using New Zealand beef in Thyro-Gold, those who use it can be sure the thyroid tissue didn't come from cows subjected to rbST. They can also be sure that the cows don't have BSE ("mad cow disease") or hoof-and-mouth viral disease, as New Zealand cows are free from these.

Based on the current certificate of analysis we have for the New Zealand thyroid tissue in Thyro-Gold, we give the powder a glowing passing mark, and the product is now in the manufacturing process. As I said, we went the extra mile in selecting the thyroid tissue and other ingredients for Thyro-Gold.

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organochlorine compound, repeated exposure caused the average body level to rise 500 times.[3] It seems wise, then, to avoid as much as possible repeated exposures to organochlorines.

Unfortunately, avoiding the compounds means avoiding sea food. The rate of reduction of organochlorines from the land is slow. Partial clearance from coastal and closed seas has been slow, but measurements of organochlorine concentrations in river fish suggest that the clearance rate is rapid in water after the source is restricted. However, samples from oceanic areas indicate a continuous input of organochlorines from land. As Loganathand and Kannan wrote, "the open ocean continues to serve as a sink for these compounds."[4]

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Podcasts of Janie Bowthorpe Interviewing Dr. Lowe Available

Janie Bowthorpe of Stop-the-Thyroid-Madness interviewed Dr. John C. Lowe on January 7 and January 14, 2010. Janie provides recordings of the interviews. You can either listen or download the recordings. The recordings are available at the following website: http://www.talkshoe.com/talkshoe/web/talkCast.jsp?masterId=62603&cmd=tc

When you reach the page, look for "Episode 8" (1 hour 36 minutes) and "Episode 9" (2 hours 7 minutes). To download the recordings, click on the download buttons; to listen to them, click on the listen buttons.

Thyroid Antibodies, Inflammation, and Thyroid Cancer

November 20, 2010

High Thyroid Antibodies and Thyroid Cancer

Ninety-eight years ago, in 1912, a paper was published on a thyroid disorder that the author named "struma lymphomatosa."[1] The word "struma" means "goiter," which is an enlargement of the thyroid gland. The word "lymphomatosa" (pronounced lim fō' mə tō' sə) means that the white cells called "lymphocytes" are spread through the tissue of a gland. The researcher who published this 1912 report was named Hakaru Hashimoto. It's in honor of his keen recognition that we now call the disorder "Hashimoto's thyroiditis."

"Elevated serum concentration of TgAb [thyroglobulin antibodies], a specific marker for autoimmune thyroid disease, was positively associated with thyroid cancer." [6,p.9]

It was 45-years later when researchers found evidence that Hashimoto's might be related to something out of kilter in the immune system. [2,p.73] In 1957, a British physician, Deborah Doniach, reported that Hashimoto's patients had high blood gamma globulin levels; the levels returned to normal after she surgically removed the patients' thyroid glands.[3] (Gamma globulin, of course, is a blood protein that reacts to antigens such as bacteria and viruses by forming antibodies against them.)

Dr. Doniach's and her collegues' work with Hashimoto's patients had been going on for several years before she reported the high levels of gamma globulin. This finding had led them to discover anti-thyroid antibodies in their Hashimoto's patients' blood.[4] In fact, that same year, 1956, the researchers found they could induce autoimmune thyroiditis in rabbits by immunizing them with rabbit thyroid extract.[5]

Today, most clinicians and thyroid patients are well aware that high blood levels of antibodies against thyroid peroxidase and thyroglobulin indicate autoimmune thyroiditis. My distinct impression is that most people who have high anti-thyroid antibodies want to get the levels down. If for no other reason, they want to avoid the possibility of the anti-thyroid antibodies cross-reacting with proteins in other tissues, setting off secondary autoimmune diseases. At this point, the scientific evidence for cross-reactivity is still debatable. However, evidence in favor of this possible health complication means that the patients' concern over this issue makes damned good sense—despite the fact of many clinicians' baffling cavalier disregard of the high antibodies.

A new study I describe below just might jar some of these supercilious clinicians into the same good sense that patients with high antibodies understandably have. It involves a health association that's far more serious than mere cross-reactivity with resulting secondary autoimmune diseases.

Thyroglobulin Antibodies and Thyroid Cancer. The researchers who recently published their results set out to determine whether thyroid cancer is associated with tests for autoimmune thyroid disease.[6] They performed fine-needle aspirations of 2500 patients in whose thyroid glands ultrasound had identified at least one thyroid nodule.

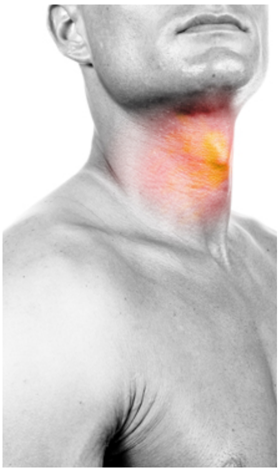
The aspirations were performed if the nodules were approximately 1 centimeter in size, or around half a centimeter if the ultrasound results raised suspicion of thyroid cancer. Before the aspirations were performed, the researchers measured the patients' levels of TSH, thyroglobulin antibodies, and thyroid peroxidase antibodies.

Pathologists analyzed the thyroid tissue taken through the fine-needle aspirations to determine whether it was cancerous. The criteria for cancer included tissue that had irregular margins, micro-calcification, a large network of blood vessels, and were "hypoechoic" (meaning that the tissue reflected fewer than normal amounts of the ultrasound waves directed at it).

Study of the aspirated tissues indicated that 202 patients had malignant thyroid nodules. Another 51 patients had cancer of tissue some distance from the aspirated nodule. That means that 253 patients tissues were malignant and 2247 patients' tissues were benign.

The 253 patients with cancerous tissue were included in a statistical analysis (multivariate logistic regression). Two positive findings resulted from the analysis: (1) thyroglobulin antibodies were positively associated with thyroid cancer, and (2) cancer was more frequent in males than females.

It's noteworthy that thyroid peroxidase antibodies were not associated with thyroid cancer. I say this because it's generally stated in the research literature that thyroid peroxidase antibodies are more "cytotoxic," meaning that they do more damage. As a result, clinicians are likely to pay more attention to patients' high thyroid peroxidase antibodies, and thyroglobulin antibodies are more likely to be disregarded. However, when considering the importance of the two types of antibodies, this study outcome is an equalizer.



Ways to Lower or Extinguish the Inflammation of Auto-immune Thyroiditis

Most people I consult with who have autoimmune thyroid disease have high levels of one or both of two destructive anti-thyroid antibodies: "thyroyid peroxidase" and "thyroglobulin" antibodies.

These two antibodies can destroy the ability of the thyroid gland to produce enough thyroid hormone for the person to remain healthy. An ultimate outcome from activity of the antibodies is hypothyroidism. And, of course, as I explain in the left column of this page, a recent study indicates that high thyroglobulin antibodies are associated with thyroid cancer, especially in men.

"Let's Just Watch it Until it Causes Health Problems." Untold numbers of patients over the years have told me that this is the advice of their clinicians: "Just wait for health problems to develop, and then we'll start you on some T4 therapy."

The problem is—and the reason the patients contact me—is that they already have health problems that appear to be due to hypothyroidism. And the patients sense that the symptoms are related to their high thyroid antibodies.

What the clinician of the typical patient doesn't seem to realize is that the patient's thyroid gland is inflamed. That is proven by the fact that the patient has high anti-thyroid antibodies. Part of the inflammation is swelling of the thyroid gland, and the swelling may cause the person to feel pressure in the front his or her neck. If the swelling is minimal, the person may not feel a moment-by-moment sense of pressure in the front of the neck. Instead, he or she may feel like swallowed food or liquid hits a bump in the front of the neck on its way down the esophagus. Some people even feel warmth or heat in the front of the neck from the inflamed thyroid gland.

Many of people with high thyroid antibodies are already troubled or even debilitated by symptoms characteristic of hypothyroidism. They often ask me, "Why should I wait to do something about it?" My answer is, "I don't think you should wait! And I simply don't comprehend your doctor's lackadaisical attitude."

It's the symptoms from the inflamed gland that drive the typical afflicted person to seek professional help. What too many get instead is a laissez-faire attitude from their clinicians, and brush offs that essentially say that the high antibodies entail no risk of at.

Not only is the inflammation the cause of the high anti-thyroid antibodies; inflammation also takes part in the formation of cancerous tumors. And as researchers state, "Chronic tissue inflammation is associated with an increased risk of tissue specific malignancy."[2,3,4] And thyroid tissue is among the tissues that are susceptible.[1,p.3]

In that inflammation or something associated with it can lead to thyroid cancer, it's prudent of your clinician(s)—and especially of you—***not*** to exercise patience. If you do, the hammer of "let's-wait-and-see" may eventually slam down on your health and well-being.

What to Do. So what's prudent to do in the way of prevention? In that inflammation is the cause of anti-thyroid antibodies and some malignancies, my approach is a strongly anti-inflammatory one.

I recommend five steps:

- Test your anti-thyroid antibodies to learn if they are high . If your clinician(s) won't order the lab tests for you, then order them yourself at discounted fees through our portal at www.directlabs.com/drlowe. (see details below).
- If you have high thyroglobulin antibodies, I believe it's important to

It is good to note that this study[6] isn't the only one to disclose this associate of autoimmune thyroid disease and cancer. Others researchers have also identified the association.[7,8,9,10,11]

A Final Word of Caution. I want to caution those who read this newsletter against a conclusion some readers with high anti-thyroglobulin antibodies might hastily reach: Having high thyroglobulin antibodies does *not* mean that you're highly likely to develop thyroid cancer.

Keep this in mind: of the 2247 patients whose ultrasounds showed nodules, only 253 had malignancies. That's only 11% of those with nodules. And if you're a woman, you might take solace in the finding that a higher percentage of men than women had malignancies.

Is the 11% high enough for you to feel anxious about the possibly of developing thyroid cancer? In general, I think it's best not to feel anxious. After all, another perspective to take is that you have a 89% chance of *not* developing cancer.

Nonetheless, in the spirit of enlightened self interest, I also feel that it's prudent to be proactive. In doing so, I encourage you to *insist* that your current clinician—or the one who replaces the current uncollaborative one you fire—help you arrange to determine whether you are cancer free despite high anti-thyroglobulin antibodies. Don't let your clinician get away with brushing aside the possible importance of high thyroglobulin antibodies. Remember, even if you never develop thyroid cancer, cross-reaction of the antibodies with similar proteins in other tissue may risk secondary autoimmune disease. In the vein of you obtaining and sustaining optimal health, your *self-directed* care of your health is of *utmost* importance, no matter what the opinion of your clinician(s).

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take a large-enough dose of thyroid hormone to lower your TSH and allow your thyroid gland to atrophy to some degree. This will provide less overall thyroid gland inflammation and fewer thyroid proteins for antibodies to attack. By the way, when I mention taking enough thyroid hormone, I do *not* refer to taking any brand of T4 alone. People do best with products that contain either T4/T3 in combination, or prompt-release T3 (not sustained-release T3.)

For a full understanding of how safe and effective thyroid hormone therapy may boost your immune system, read the pdf chapter from *The Metabolic Treatment of Fibromyalgia*. It's available through the publisher as a standalone pdf chapter. (When you reach the e-chapter page, scroll down to the immune chapter: Chapter 3.13 Immune Dysregulation.)

- Make sure you have enough anti-inflammatory cortisol . Today, salivary free cortisol levels is the superior lab test to do—despite the fact that many clinicians are stuck in mid-20th century thinking and unscientifically "don't believe in salivary testing." Leave these anachronistic clinicians stuck in the ancient past, like the snails, gophers, and saber-tooth cats preserved in the La Brae tar pits of Los Angeles. Instead, move on and avail yourself of modern laboratory scientific advancements and get salivary free cortisol levels, not the total blood cortisol levels.

  Your daytime and nighttime free saliva cortisol levels should look close to the graphed levels published in our August 27, 2010 newsletter.

- Adopt and stick to an anti-inflammatory diet. This means either consuming either a cave person diet or one of the many rich Mediterranean diets that include foods like those in this photo. These diets are so varied and so health-inducing and health-sustaining that once you adopt them for your own, you're likely to find the pro-inflammatory traditional American-type diet repugnant and easy to reject.

- Take an array of anti-inflammatory nutrients, herbs, and other botanicals. Some include omega-3 fatty acids; bromelain; Boswellia; superoxide dysmutase; ginger; turmeric; glucosamine; chondroitin; and a strong raw-foods, organic multivitamin supplement like Franconia's New Life Multi.

A final word: *Educate yourself and direct your own health care.* Some Dr. Marcus Welby's still exist, but they are *far* too few, and you have only a slim change of finding one to take care of your health-care needs. And besides, these extraordinary doctors, just as we all do, harbor mistaken and misguiding beliefs. Investigate the veracity of anything and everything that *any* clinician tells you. As troubling as it may feel at first, it's *you* who is your own best doctor today.

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Hypothyroidism and Ovarian Cysts. Desiccated Thyroid & Thyroid Antibodies.

November 27, 2010

Multiple Ovarian Cysts as a Major Symptom of Hypothyroidism

The case I describe below is of importance to women with polycystic ovaries. If they have evidence, such as a high TSH, that conventional clinicians accept as evidence of hypothyroidism, they may fair well. But the TSH is *not* a valid gauge of a woman's tissue thyroid status. Because of this, she may fair best by adopting self-directed care. At any rate, for women with ovarian cysts, this case is one of extreme importance.

In 2008, doctors at the gynecology department in Gunma, Japan reported the case of a 21-year-old women with primary hypothyroidism. Her doctor referred her to the gynecology department because she had abdominal pain and her abdomen was distended up to the level of her navel.

At the gynecology clinic she underwent an abdominal ultrasound and CT scan. These imaging procedures showed multiple cysts on both her right and her left ovary.

The woman's cholesterol level and liver function were increased. She also had a high level of the muscle enzyme (creatine phosphokinase) that's often high in hypothyroidism. Blood testing also showed that the woman had primary hypothyroidism from autoimmune thyroiditis.

It is noteworthy that the young woman's ovarian cysts completely disappeared soon after she began thyroid hormone therapy. Other researchers have reported girls with primary hypothyroidism whose main health problems were ovarian cysts or precocious puberty. But this appears to be the first case in which a young adult female had ovarian cysts that resulted from autoimmune-induced hypothyroidism.

The researchers cautioned clinicians: "To avoid inadvertent surgery to remove an ovarian tumor, it is essential that a patient with multiple ovarian cysts and hypothyroidism be properly managed, as the simple replacement of a thyroid hormone could resolve the ovarian cysts."[1]

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Does Taking Desiccated Thyroid Cause or Worsen Autoimmune Thyroid Disease?

Fairly often, someone asks me whether taking desiccated thyroid is likely cause or worsen autoimmune thyroid disease. A few of these people have become concerned because of a rabbit study they've heard about. I've read summaries of this study, and typically the summaries state: "Rabbits developed autoimmune thyroid disease after being injected with thyroid extract from other rabbits."

After reading these summaries, some people understandably asked, "The rabbit developed autoimmune thyroid disease after being exposed to thyroid extract. Doesn't this mean that if I expose myself to thyroid extract in desiccated thyroid, it can cause me autoimmune thyroid disease in me? Some people who already had high thyroglobulin or peroxidase antibodies asked, isn't desiccated thyroid likely to stoked up these antibodies in me?

In the studies these people mention, the researchers did inject rabbits with extracts of rabbit thyroid glands. And the injections led to anti-thyroid antibodies in the injected rabbits and damage to their thyroid glands.

However, the injections also included saline (salt) and another substance called "Freund's adjuvant."[4,p.1295] The importance of this latter ingredient is that it's a *powerful* booster of the immune response to antigenic stimuli. Laboratory researchers use it to augment antibody responses to antigens that might otherwise provoke only faint antibody reactions. The adjuvant is *severely* toxic. Researchers are banned from using it in humans, and they use it sparingly in laboratory animals.

Because the rabbit thyroid extract was mixed with saline and Freund's adjuvant, I'm curious as to whether the injected thyroid extracts alone would have provoked antibodies against thyroglobulin. Maybe it would not have.

However, there's also another important consideration. I've talked with people from the companies that manufacture desiccated thyroid products, and they've told me that they don't measure the amount of the proteins thyroglobulin and peroxidase in the thyroid powder they use in their products.

Nonetheless, the important point is that the thyroglobulin and peroxidase in desiccated thyroid are *proteins*. Ingesting these proteins may not increase antibody activity for this reason—protein-digesting enzymes in the GI tract are likely to decompose the proteins into amino acids. And although the amino acids may then absorb into the body, they aren't likely to recompose themselves into proteins that function as antigens to stoke up antibody reactions against them.

I know of only one study in which researchers actually tested the hypothesis that desiccated thyroid might affect patients' autoimmune thyroid disease. The researchers switched patients with the disease from synthetic T4 to desiccated thyroid for a year. Other patients continued to use synthetic T4. At the end of the year, the two groups of patients did *not* differ in measures of autoimmune thyroid disease; desiccated thyroid had not worsened any immune measures.[5]

To answer this oft asked question, then, ingesting desiccated thyroid is *not* likely to cause or worsen autoimmune thyroiditis.

Tammy@drlowe.com

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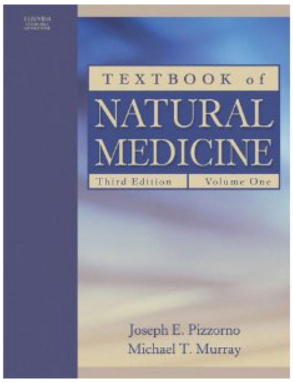

My Fibromyalgia Chapter for the 4th Edition of the *Textbook of Natural Medicine*

At 1 am, Tuesday, October 12, 2010, after three days isolated in a motel in Juno Beach, Florida, I completed a three-month long project. That project was to revise and update my chapter on fibromyalgia for the forthcoming 4th edition of the *Textbook of Natural Medicine*.

This 2-volume textbook is edited by the brilliant and prolific naturopathic physicians Dr. Joseph Pizzorno and Dr. Michael Murray. They had given me the privilege of writing the fibromyalgia chapter for the 3rd edition and to revise it for the 4th edition. The 3rd edition of the *Textbook* was published in 2006, and the 4th edition will be published in 2011.

My updating of the fibromyalgia chapter involved several steps. First, I thoroughly reviewed the fibromyalgia research published in journals and books since 2005.

Second, I learned something important from my thorough review of the available research: that is, nothing has changed my former conclusions about fibromyalgia; in fact, additional studies, more strongly support my original conclusion: ***that the main underlying mechanism of most people's fibromyalgia is too little thyroid hormone regulation, complicated in most cases by other metabolism impeding factors.***

In two reinforcing studies, I found that fibromyalgic women had low metabolic rates compared to matched healthy controls (2006a and 2006b). I also found that the patients' lower metabolic rates were *not* due to lower levels of physical activity.

In the chapter for the 4th edition of the Textbook, I added some new diagnostic and treatment procedures. These can help both fibromyalgia patients and the clinicians who care for them by dealing with their inadequate thyroid hormone regulation.

My review of the last 5 years of fibromyalgia publications also strengthened my belief of something else of importance to fibromyalgia patients: that is, the failed rheumatology fibromyalgia research paradigm continues to contribute *nothing* to enable fibromyalgia patients to recover their health. Fortunately, however, many natural medicine clinicians know the truth about fibromyalgia's relation to thyroid conditions; these clinicians have helped thousands of fibromyalgia patients to recover their health.

My reevaluation of the fibromyalgia research literature, and my personal experiences also show the following: The rheumatology paradaigm of fibromyalgia has utterly failed to unveil the underlying causes of fibromyalgia symptoms. Now, some 40 years after beginning to study fibromyalgia, the rheumatology paradigm of fibromyalgia is now little more than a sycophant of Big Pharma, focusing on obtaining research grants to test expensive and potentially harmful drugs. The drugs will *never* get a fibromyalgia patient well, and will do little if anything to reduce patients' pain.

I'm grateful to Dr. Pizzorno and Dr. Murray for allowing me to contribute the revised chapter to the 4th edition of their nonpareil *Textbook of Natural Medicine.* I believe this 2-volume book should be close at hand for both clinicians and health care consumers who know the value of wisely combining the best of conventional and natural medicine.

Kristin Thorson's Magazine Interview

Fibromyalgia Network
A journal for patients, their families, and physicians
Dealing with Frustration and Fears
Tame charge of these angry emotions
Power Up Your Body's Defenses

For more than 20 years, I've known of a person who has diligently worked for the well-being of fibromyalgia patients. She is Kristin Thorson, originally educated as a chemical engineer. Her work on behalf of fibromyalgia patients has been truly extraordinary.

Among Kristin's exceptional contributions to the cause of fibromyalgia patients has been her arranging for the financial funding of many fibromyalgia studies. Without the funding she arranged, we would be bereft of some of the

Tonight!

Bette Dowdell & Dr. Lowe: Live Teleseminar on Dr. Lowe's Personal Thyroid Story

Tammy Lowe

Tonight, December 14, 2010, Dr. Lowe will be the guest on Bette Dowdell's teleseminar. (See the beige box below for the time of the teleseminar for your time zone.) We all invite you to listen in live.

I know that many of you are already familiar with Bette's popular website Too Pooped to Participate. She often sends out her free e-zine and she offers her e-books such as Pep for the Pooped. We admire Bette partly because she's generously passed forward to others-in-need what she learned in recovering her own health after conventional medicine failed her.

For the teleseminar tonight, Bette has generously written:

> "Tonight we're honored to have Dr. John C. Lowe with us to tell his thyroid story. Dr. Lowe has become a leading voice in the treatment of thyroid problems so you'll be hearing a voice of considerable authority."

The link for the teleseminar is http://instantteleseminar.com/?eventid=14918178

When you reach the page, either use the phone number or click the go arrow to listen by web on your computer.

You can listen live to Bette's teleseminar with Dr. Lowe by telephone or through your computer.

(1) **Webpage**. Bette's teleseminar webpage:

http://instantteleseminar.com/?eventid=14918178

(2) **Listen by Phone**. The phone number to call is *623-255-3832*. (The backup phone # is 775-335-3180.) You'll also need the conference ID, *223057#*, which is also on her teleseminar webpage.

(3) **Listen by Computer**. Just click on the go arrow (see our copy of Bette's webpage above.)

(4) **Date**. The date is Tuesday, December 14th, 2010.

(5) **Time**. The time is 6:00 pm Pacific Time. That's the same as 7:00 pm Mountain Time, 8:00 pm Central Time, and 9 pm Eastern Time.)

(6) Please call in a few minutes early so Bette knows you're there. Please do not give this code to anybody else.

(7) You may not have the latest version of Adobe Flash Player on your computer. Adobe provides the latest version for *free*. You can easily download it: http://www.adobe.com/software/flash/about/. Click the orange button that reads, "Install NOW: It's free."

(8) **Submit a Question**. At Bette's teleseminar webpage, you'll see a "Q&A" box at the lower left of the page.

Dr. Lowe Interviewed by Dr. Joseph Mercola on Skype

by Tammy Lowe

This Thursday, December 16, 2010, Dr. Joseph Mercola will interview Dr. John C. Lowe through Skype. The Skype interview provides both sight and sound. The two doctors have allowed up to two hours for the interview. Before the interview is released, however, it will be edited to a much shorter time and possibly posted to YouTube.

information that has enabled us to better understand the nature of fibromyalgia. I'm personally grateful for her exceptional humanitarian work on behalf of fibromyalgia patients.

Kristin's organization is the Fibromyalgia Network. I encourage you to visit the Network's website and subscribe to their *Fibromyalgia Network* magazine (see the cover above).

Kristin contacted me last week, prompted in part by a study report conducted by a rheumatologist in Italy, Dr. Bazzichi. I hadn't heard of the report and I'm grateful to Kristin for bringing it to my attention.

The title of Dr. Bazzichi's report makes clear the implications of her study findings: "Thyroid autoimmunity may represent a predisposition for the development of fibromyalgia?"[1] (I'll soon provide details of the study and its results.)

In 2005, Kristin wrote an article in the *Fibromyalgia Network* magazine about metabolism and fibromyalgia. She is now writing another article on that topic. Her focus is the research findings of Dr. Bazzichi and my research teams' work on the thyroid-related bases of fibromyalgia. Kristin and I spent some four hours on the telephone discussing the topic while she conducted an interview.

Kristin Thorson
Fibromyalgia Network
www.fmnetnews.com
7371 E Tanque Verde Rd
Tucson, AZ 85749
TEL: (800) 853-2929
FAX: (520) 290-5550

We will send out notice of when Kristin's article will be published in the *Fibromyalgia Network* magazine. I'm immensely grateful to Kristin for giving the thyroid line of research due attention after so many years of censorship by others.

Reference

1. Bazzichi, L., Rossi, A., Zirafa, C., et al.: Thyroid autoimmunity may represent a predisposition for the development of fibromyalgia? *Rheumatology Int.*, 2010, Nov 18.

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Dr. Lowe is taking the opportunity to discuss three important issues: (1) his personal protest of the British Thyroid Association's patent scientifically false statements about Armour Thyroid and T4 replacement therapy; (2) various misleading statements the organization continues to keep on its website that are contradicted by facts; and (3)the organizations scientifically indefensible preference for T4 replacement by failing to point out findings in studies that favor T4/T3 therapies rather than T4 alone.

Dr. Lowe has long admired Dr. Mercola for his horn-locking approach in showing the harm to human health from various sources, most of which lead back to funding of conventional medicine by corporations such as Big Pharma.

We will let you know when this Skype interview is accessible online.

Where will the conversation between Dr. Mercola and Dr. Lowe go from there? We'll see.

Tammy@drlowe.com

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We provide educational consulting to both patients and clinicians. Phone us at 603-391-6061, or preferably, write to us at Tammy@drlowe.com. Our fax number is 303-496-6200. **—*Tammy Lowe***

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Short- and Long-Term Protection from a Nuclear-Plant Meltdown

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| Meltdown: Is Potassium Iodide Enough? |

| Mercola/Lowe Interview |

Meltdown in Japan: Is Potassium Iodide Enough?

March 16, 2011

Yesterday evening, Tuesday, March 15, 2011, the Chicago Tribune and the Associated Press[1] released interesting consumer news related to the nuclear crisis in Japan. They noted that potassium iodide supplements can protect the thyroid gland if taken before or shortly after a radiation exposure. This is well-known enough that as of Tuesday, stores were selling the supplement rapidly or were already completely sold out.

A reporter interviewed Troy Jones, President of nukepills.com in Mooresville, N.C. He told them that in a normal four-day period, he'd sell only 100 packages of potassium iodide. But in the last four days, he's sold 6,500 orders. Most of the orders have come from US West Coast states, including Washington, Oregon, and California.

But even on the US East Coast, health department personnel have reported rising public interest in nearby nuclear power plants. "A Pennsylvania hotline that normally gets five to 10 calls a week about storing the [potassium iodide] pills has fielded 85 such inquiries in the past two days."[1]

The news report stated the obvious: These US customers are people "who want to protect themselves from any Japanese radiation."[1]

But concerns about radiation exposure aren't limited to the US consumers. A reporter quoted Raphael Karunditu, President of California-based Gamma-Scout: "The phone has been ringing off the hook," he said. "We have hundreds-upon-hundreds of orders, and our partner in Germany is talking about thousands of orders at his site."[1]

Authors of the news report point out that Russians have a vivid memory of the Chernobyl disaster 25 years ago. And concern over the ongoing nuclear crisis in Japan is reflected in sales of potassium iodide products. "Pharmacies in Vladivostok, a major port just west of Japan, had run out of the pills,"[1] the report said.

The Information Below Reaches Far Beyond the Crisis in Japan. People in Japan (many of whom read drlowe.com) can use the information I provide below. Also, if winds carry radioactive elements from Japan to other countries, the information can benefit people in those countries.

However, even if radiation from Japan doesn't reach the US, we have 104 nuclear power plants of our own. Recent climatic and other crises make one or more human-harming nuclear disasters in the US far from unlikely. A close nuclear disaster not only threatens us with soon-occurring thyroid cancer; it also poses other serious health risks literally for decades to come. I explain after mentioning the immediate value of potassium iodide.

Radioactive Iodide Released in a Nuclear Plant Meltdown

Many people are obviously aware that iodine-131 is a radioactive element released into the environment during nuclear meltdowns. Most people are probably also aware that potassium iodide can block the entry of radioactive iodide into the thyroid gland. If taken quickly enough, the potassium iodide can prevent thyroid cancer. Lots of folks fear that radiation-induced thyroid cancer is fatal, but hold on; information below may assuage the fear (see A positive note below). If consumers weren't aware of these issues, of course, sales of potassium iodide wouldn't have skyrocketed in the last several days.

It is entirely proper to focus on protecting one's thyroid gland as the initial effort before or upon radiation exposure. Consider a 2004 report in Indopedia about the "acute effects" of radiation exposure following the 1986 Chernobyl accident:

"Some children in the contaminated areas were exposed to high thyroid doses . . . because of an intake of radioactive iodine, a relatively short-lived isotope, from contaminated local milk. Several studies have found

***Children and gestating fetuses are most vulnerable to thyroid cancer from exposure to radioactive iodine.* Because of this, protecting their thyroid glands with potassium iodide is a high priority.**

Doses of potassium iodide for children & infants

Continued from left-hand column

Radioactive Elements Other than Iodine-131

Many people, then, are aware of the potential of radiation-induced thyroid cancer and the protection given by potassium iodide. Fewer people, though, seem to be aware that radioactive forms (isotopes) of other elements are also released into the environment during a nuclear meltdown. Two elements of major concern are strontium-90 and xenon-135. Poisoning by xenon-135 was a major source of harm to people during and after the Chernobyl disaster.[2,p.421] But other radioactive elements are also long-lived. Noteworthy examples are xenon-133 and caesium-137.[7]

Long-term avoidance of radioactive elements from a meltdown. Keeping potassium iodide on hand is important during early exposure to radiation. However, our efforts to reduce harm from radiation should also be long-term.

Strontium-90, for example, is an abundant by-product of nuclear fission. If it escapes into the air during a meltdown, wind currents can carry it to far distances. Eventually, gravity, rain, or snow causes the wind to drop the strontium-90 from the air onto the earth.

On the ground, the strontium-90 contaminates the grass in cow pastures and plants grown for food, such as corn and wheat. When animals such as cows consume the strontium-90, and humans consume parts of the cows and drink their milk, the strontium-90 ends up in many of our tissues. (Of the total body content of humans, however, 99% is in bones and teeth.[4,5]) Of course, seafood and birds may also take in the radioactive element, and it can contaminate water.[4,5]

The importance of avoiding the intake of strontium-90 by any route was highlighted in a 2011 health policy report.[6] The report was based on measurements of the strontium-90 levels in 85,000 teeth. Researchers collected the teeth from Americans born during the nuclear bomb-testing years.

The researchers reported an eye-opening finding: Compared to teeth from people who didn't die of cancer, the average strontium-90 content of teeth from people who died of cancer was significantly higher. They concluded, "This discovery suggests that many thousands have died or will die of cancer due to exposure to [nuclear] fallout, far more than previously believed."[6,p.1] (Italics mine.) This may apply to people exposed to radiation from nuclear plant meltdowns.

A 2004 Indopedia report about the Chernobyl accident is important to a proper perspective on the priorities of different radioactive elements. The authors wrote: "Right after the accident, the main health concern involved *radioactive iodine, with a half-life of eight days. Today, there is concern about contamination of the soil with strontium-90 and caesium-137, which have half-lives of about 30 years. The highest levels of caesium-137 are found in the surface layers of the soil, where they are absorbed by plants and mushrooms and enter the local food supply.* Recent tests have shown that caesium-137 levels in trees of the [Chernobyl] area are continuing to rise." (Italics mine.)

The point, of course, is the matter of extreme differences in the half lives of different radioactive elements. The lesson is, focus first on radioactive iodine, but don't forget to avoid long-term the more long-lived radioactive elements. The long-term avoidance involves abstaining from ingesting potentially-contaminated plant and animal foods.

Does Taking Thyroid Hormone Protect Against Radioactive Iodine?

that the incidence of thyroid cancer among children in Belarus, Ukraine, and Russia has risen sharply."[7] (Italics mine.)

A positive note. The Indopedia report[7] contains a note that may temper some people's fears: "The childhood thyroid cancers that have appeared [in and near Chernobyl] are of a large and aggressive type, and if detected early, can be treated. Treatment entails surgery followed by iodine-131 therapy for any metastases." The authors continue, "To date, such treatment appears to have been successful in all diagnosed cases."

This note indicates that if potassium iodide fails us, rapid diagnosis and effective treatment of the thyroid cancer can prevent a lethal outcome. To avoid well-known potential problems in consulting endocrinologists, I recommend that patients consult ear-nose-and-throat specialists, who in general have a more collaborative and friendly toward their patients.

This note indicates that if potassium iodide fails us, rapid diagnosis and effective treatment of the thyroid cancer can prevent a lethal outcome. Of course, many people would anticipate well-known potential problems in with consulting endocrinologists. Because of this, I recommend that patients consult ear-nose-and-throat doctors who specialize in thyroid surgery. They generally are friendlier and more collaborative with their patients.

When and when not to take potassium iodide. As I said above, if taken in time, potassium iodide blocks the thyroid gland's uptake of radioactive iodine. It's important, though, to take potassium iodide only during acute radiation exposure.

Severe acute radiation exposure usually kills people through systemic infections.[10] This is due to impairment of the immune system and damage to the lining of the GI tract and lungs. It's possible that potassium iodide can provide some protection of the GI and respiratory tract linings. The protection would come from the potassium iodide blocking some secretion of radioactive iodine in the mucous membrane linings of the GI and respiratory tracts.

However, it's not likely that potassium iodide would protect us in any other ways. And, then, we still have strontium-90, xenon-135, and other radioactive elements to protect ourselves from. Our concern shouldn't be restricted to the time of acute exposure during a meltdown; it should extend many years into the future.

When strontium-90 enters the body, it's taken up mainly by bone and teeth.[4,5] It's mainly in bone where the radioactive element does damage. Xenon-135 disperses throughout and damages the whole body.

During a meltdown, we can reduce the amounts of strontium-90 and xenon-135 that enter our bodies. We can do so by confining ourselves to a structure such as a house that impedes the flow of radioactivity. We can also reduce our intake by bathing and either washing or disposing of contaminated clothes. It's also possible that taking small amounts of calcium at frequent intervals will reduce the strontium-90 entry through the GI tract. This is possible because calcium in the GI tract competitively reduces strontium absorption into the blood.[3.p.447]

The CDC's[8] recommended dose schedule is as follows:

Adults: one 130 mg tablet, two 65 mg tablets, or 2 mL of solution.
Breastfeeding women: one 130 mg tablet.
Children 3 to 18 years old: one 65 mg tablet or 1 mL of solution.
Children who are adult size (150 pounds or more): one 130 mg tablet, despite age.
Infants and children between 1 month and 3 years old: 32 mg (½ of a 65 mg tablet, or ½ mL of solution). The dose is recommended for nursing and non-nursing infants and children.
Newborns from birth to 1 month of age: 16 mg (¼ of a 65 mg tablet or ¼ mL of solution). The dose is recommended for both nursing and non-nursing newborn infants.

The CDC emphasizes that no additional protection is provided by larger doses of potassium iodide. Also, taking potassium iodide for long times risks harm to oneself setting off the Wolff-Chaitoff buffering effect. This effect leaves some people with Hashimoto's thyroiditis.

Also, some people with severe cortisol deficiencies may have low body sodium but high potassium levels.[12] In using potassium iodide properly (usually only over several days), the potassium intake would be small. Nonetheless, in extreme case, a cortisol deficient person may already have high potassium. This person might be harmed by taking additional potassium as potassium-iodide.

Continued in right-hand column

Many people take enough thyroid hormone to lower their TSH levels below the lower limit of the reference range. A low TSH level usually reduces the size of the thyroid gland. The gland also takes up less iodide and produces less thyroid hormone, although it still produces some. Perhaps an atrophied gland also takes up less radioactive iodine.

Question arises, then: Are people who take TSH-lowering doses of a thyroid hormone protected to some degree from radioactive iodine-induced thyroid cancer? And what about people who don't take thyroid hormone? They are dependent on their thyroid glands taking up enough iodide to produce sufficient amounts of thyroid hormone. Because of this, do they take up more radioactive iodine, too, making them more susceptible to thyroid cancer?

I haven't found studies showing that people who take TSH-lowering doses of thyroid hormone are better protected from thyroid cancer induced by radioactive iodine. However, thyroid cancer patients in general prevent recurrences by taking TSH-suppressive doses of thyroid hormone. And during the T3 suppression test, which is seldom done anymore, most patients who took 75 mcg[13] to 100 mcg[14,p.1708] of T3 for a week or so had a decrease of radioactive iodine by the thyroid gland.

It may be, then, that other people who take TSH-suppressive doses are better protected than others from iodine-131 induced thyroid cancer.[9]

Protection by a Strong Immune System

As I wrote above, death from radiation exposure appears to result mainly from systemic infections.[10] On principle, the people most susceptible to infection are those with weak immune systems.

As I showed in *The Metabolic Treatment of Fibromyalgia*,[11,pp.635-680] parts of the immune system are impaired in most people who are hypothyroid or thyroid hormone resistant. Effective thyroid hormone therapy (usually not T4 replacement!) is essential for these people to recover normal or even stronger immune function. In addition, though, they—like everyone else—would be prudent to also protect themselves in another way: by taking an array of dietary supplements that studies show boost immune efficiency.

A Final Thought

I believe another piece of news from the *Chicago Tribune* and the Associated Press[1] is encouraging: In the last several days, ". . . companies that sell Geiger counters have been overwhelmed with orders." This is crucially important, as potassium iodide will serve us only during acute radiation exposure. A Geiger counter can signal when it's proper to take potassium iodide.

The CDC tells us that local emergency management or public health officials will let us know when we can safely stop taking potassium iodide.[8] Some of us, however, are more trusting of our own judgment and would prefer to supplement the advice of public officials with a report by our personal Geiger counters. The Geiger counter can let us know when the radiation level has safely dropped; it can thus enable us to avoid harm that occasionally results from human error of public health officials.

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Tammy@drlowe.com

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303-496-6200. —***Tammy Lowe***

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Phone Calls About Armour Thyroid

by Dr. John C. Lowe

April 2, 2003

Latest Updates to drlowe.com

The April 2002 issue of *Let's Live* magazine contains a letter to the Editor by Ms. Barbara Porell, a fibromyalgia patient. In her letter, she describes her 50% improvement after using Armour Thyroid for two months. *Let's Live* appropriately gave our phone number and web address as the source of information on the metabolic treatment for fibromyalgia. As a result, Ms. Porell's letter has set off a deluge of phone calls over the last week to our Center for Metabolic Health.

Many of the patients who have called have asked only one question: Where can I purchase Armour Thyroid? These patients apparently have the impression that Armour Thyroid is a magic pill that enabled Ms. Porell to improve. Understandably, the magic-pill misconception motivates these patients to want to try Armour.

We must emphasize, however: Recovery from fibromyalgia (or any other set of symptoms caused by hypothyroidism or thyroid hormone resistance) is not merely a matter of taking thyroid hormone; it's a matter of using the proper treatment protocol. True, many patients such as Ms. Porell improve somewhat just by taking the proper form of thyroid hormone. But as Ms. Porell makes clear, she too is aware that more is involved than just taking the hormone. (See our report on her letter.) Because more is required, it would be derelict of us to merely refer patients to sources of Armour.

Patients must also be aware of something else: As doctors, we can't merely refer patients we don't know to sources of thyroid hormone products. If we did, we would imply acceptance of liability for the well-being of those patients. *We can refer patients to obtain thyroid hormone* only *if those patients are officially under our care*. Because of this, please phone our Assistant, Bethany Bushman, *only* if you want to become a patient of ours. Please don't phone her to ask where to purchase Armour Thyroid or any other brand of thyroid hormone. We appreciate your cooperation.

News Report on Ms. Porell's Letter-to-the-Editor of *Let's Live* Magazine

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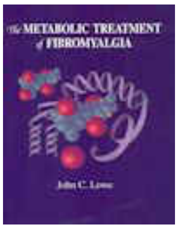

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Seattle-Area Seminar a Success | Dr. John C. Lowe and Vicky Massey, LMP to Speak in Seattle, Washington Area | Negotiations to Study Blood Coagulation | St. Amand Advocate Apologizes to Dr. Lowe to Avoid Libel Suit | Let's Live Magazine Publishes Article on Our Work | Vicky Massey, LMT Appointed to FRF Board | Official Statement of the Fibromyalgia Research Foundation: "T4 Replacement Therapy: An Obstacle to Recovery from Fibromyalgia" | Advance Magazine to Publish Article on Metabolic Rehab | Open House: Center for Metabolic Health, Boulder, Colorado |

Archived News (2001)

Jackie Yellin to Speak in New Hampshire | Sticking Out Our Necks A Newsletter of Vital Importance | Dr. Lowe & Dr. Honeyman-Lowe to Speak in Pittsburgh With Mr. Richard Finn | Dr. Lowe & Dr. Honeyman-Lowe: Board Members of Thyroid UK | Political Tyranny Prevails in England | Potency of Compounded T3 Found Unreliable | Dr. Lowe to Speak at the Convention of the NAMTPT | Dr. Lowe to Appointed to Board of Advisors of NAMTPT | Drs. Lowe & Honeyman-Lowe to Speak in France | Follow-up to France Trip | Text of Speech in France |

Archived News (2000)

Conference in Warwick, England | Dr. Lowe Appointed to Editorial Board of JBMT | Dr. Lowe & Dr. Honeyman-Lowe to Speak & Evaluate Patients Santa Fe, New Mexico |Radio Interviews & Chat Rooms | Dr. Lowe & Dr.Honeyman-Lowe to Speak in France | French Medical Journal Publishes Papers By Dr. Lowe & Dr. Honeyman-Lowe | Two New Books on Thyroid Disease |

Archived News (1999)

Mary Shomon's New Book | Interview with Dr. Lowe | Patients Take Endocrinology to Task | Dr. Lowe's Letter to Gov. George W. Bush about Texas Dietitian Act |

Fibromyalgia Research Foundation

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The views expressed at drlowe.com are based on studies conducted by Dr. John C. Lowe, Dr. Gina Honeyman-Lowe, Jackie Yellin, and other researchers through the Fibromyalgia Research Foundation.

Systematic Open Trials | Double-blind Clinical Trials | Thyroid Status Studies |
A Case-control Follow-up Study | Theoretical Papers | Other Papers |

Nutrition

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Science & Logic

Introduction to Our Online Science & Logic Journal

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Vicky Massey

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Dr. John C. Lowe About Dr. Lowe

Commentary by Dr. Lowe

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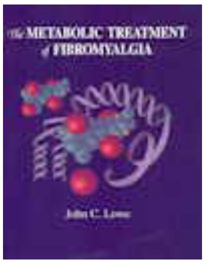

The Metabolic Treatment of Fibromyalgia
by Dr. John C. Lowe
Readers' Comments

Fibromyalgia & Thyroid Disease

Dr. John C. Lowe, et al.

Presented and discussed in Grenoble, France, May 6 (conference of the French Fibromyalgia Association of Région Rhône-Alpes) and in Toulon, France on May 11 (at the Centre Hospitalier Intercommunal), 2000. Published: Lowe, J. C., et al.: Thyroid disease and fibromyalgia syndrome. *Lyon Méditerranée Médical: Médecine du Sud-Est.*, 36(1):15-17, 2000.

The clinical features of fibromyalgia syndrome (FMS) and hypothyroidism are virtually the same (1,2,3,4,5,6,7,8,9,10). The most common symptoms of FMS are also common symptoms of hypothyroidism, and the objective abnormalities of FMS are also objective abnormalities of hypothyroidism. The symptoms and objective abnormalities of hypothyroidism are mediated by inadequate thyroid hormone regulation of cell function. Inadequate thyroid hormone regulation also plausibly mediates the documented features of FMS (11).

Hypothyroidism in FMS

Primary Hypothyroidism. The estimated incidence of hypothyroidism in FMS is higher than in the general public. The reported incidence of primary hypothyroidism in the general non-elderly USA population varies between 1% (12) and 5% (13). Laboratory thyroid function testing suggests that the incidence of primary hypothyroidism in FMS is 10% to 13% (14, 15, 16, 17, 18).

Anti-thyroid Antibodies. Aarflot and Bruusgaard measured thyroid microsomal antibodies in 737 men and 771 women who ranged in age from 40-to-42 (19). Subjects with chronic widespread musculoskeletal complaints had a significantly higher incidence of antibodies than did subjects without such complaints (16.0% versus 7.3%, $p<0.01$). The prevalence of antibodies was significantly higher in women than men (20.4% versus 11.6%, $p = 0.02$). It is noteworthy, however, that laboratory thyroid function test results did not differ significantly between the two groups. The investigators wrote that their results suggest that patients with microsomal thyroid antibodies may have symptoms due to subnormal thyroid hormone regulation of cell function before thyroid gland dysfunction is detectable by tests of thyroid hormone and TSH levels. The researchers implied that many patients diagnosed with FMS may in fact have chronic, widespread pain due to impaired thyroid gland function revealed only by increased titers of thyroid microsomal antibodies. If this is true, then the incidence of primary hypothyroidism among FMS patients may be higher than the 10% to 13% suggested by measures of TSH and thyroid hormone levels.

Central Hypothyroidism. The incidence of central hypothyroidism, involving hypothalamic or pituitary dysfunction, in the USA population at large is about 0.00021% (12). Our research group has found that of 92 sequential unselected FMS patients, 40 patients (43.5%) had laboratory test results consistent with central hypothyroidism (16, 18). Other researchers have also reported high incidences of test results consistent with central hypothyroidism (20,21).

Thus, the incidence of primary hypothyroidism among FMS patients may be 2 to 10 or more times higher than in the USA population at large. The incidence of possible central hypothyroidism, however, may be 250,000 times higher. If we trust that thyroid function test results are reliable, we are compelled to reach a conclusion: If 10% of FMS patients have primary hypothyroidism, and 44% have central hypothyroidism, the total percentage of FMS patients with hypothyroidism is 54%.

Thyroid Hormone Resistance

Many researchers and clinicians consider the term "thyroid disease" to include only pathological processes that occur 1) within the thyroid gland itself, or 2) in other tissues, such as the pituitary gland, and indirectly result in subnormal function of the thyroid gland. However, this definition may be too narrow. In 1967, Refetoff et al. provided convincing evidence of partial cellular resistance to thyroid hormone in humans (22). Since then, a great volume of studies of human thyroid hormone resistance has accumulated. Also, mutations in the c-erbAß gene on chromosome 3 (which codes for the ß1 T3-receptor) have been shown to be the underlying mechanisms of general resistance to thyroid hormone (23). (The mechanisms of resistance in most afflicted patients remain unknown.) In some thyroidology textbooks, thyroid hormone resistance is grouped under "Special Topics in Thyroidology." However, it can be argued that thyroid hormone resistance should be classified as a subset of thyroid disease. As in central hypothyroidism, which is classed as a thyroid disease, thyroid gland function is indirectly altered in two classifications of thyroid hormone resistance. Also as in primary and central hypothyroidism, patients with symptoms and signs caused by thyroid hormone resistance can be effectively treated with thyroid hormone (albeit in higher than physiologic dosages, called "supraphysiologic" dosages).

Thyroid Hormone Resistance and FMS. As far back as the late 1980s, I (JCL) was puzzled as to why euthyroid FMS patients (those with normal thyroid test results) had identically the same hypothyroid-like symptoms and signs as did hypothyroid FMS patients. In searching for an answer, I came into communication with thyroid hormone resistance researchers. One of these, Steve Usala, had established a link between the c-erbAß gene and thyroid hormone resistance (24). He was also first to discover a mutation in the gene (25). (More than 100 different mutations in the gene have now been discovered (11).) Based on communication with Usala and other thyroid hormone resistance researchers, in 1990, my colleagues and I treated 77 euthyroid female FMS patients with T3 (as part of comprehensive metabolic treatment).

This treatment was based on our hypothesis that the patients had partial cellular resistance to thyroid hormone (26). Of the 77 patients, 19 (25%) did not feel that T3 had improved their status. They were withdrawn from use of the hormone. The remaining 58 patients (75%) reported that their symptoms were improved to varying degrees. For the group, the difference between pre- and post-treatment algometer scores (mean of the pressure/pain threshold of 18 tender points) was highly significant (p:< 0.0005). The mean pressure/pain threshold of the 18 tender point sites was significantly higher (improved) after T3 treatment. Effective dosages of T3 ranged from 75 µg. to 150 µg.

Most patients improved with dosages between 81.25 µg. and 100 µg. (Normal replacement dosages were reported to be from 25-to-75 µg.) Since that early open trial, we have continued to treat euthyroid FMS patients on the assumption that they have thyroid hormone resistance. We find that approximately 75% of euthyroid FMS patients markedly improve or completely recover when treated with what we term "metabolic rehabilitation." The treatment involves the use of T3, exercise to tolerance, wholesome diet, nutritional supplements, physical treatment, and cessation of the use of metabolism-impeding medications.

Most euthyroid patients improve only with supraphysiologic dosages of T3. We are convinced that the patients who improve or recover with supraphysiologic dosages of T3 have cellular resistance to thyroid hormone. We conclude that a patient has thyroid hormone resistance when four criteria are met. The patient:

(1) is euthyroid before beginning the use of T3, according to thyroid function test results, including a TRH stimulation test;

(2) markedly improves or completely recovers from hypothyroid-like FMS symptoms and signs with supraphysiologic dosages of T3;

(3) after beginning T3 therapy has an extremely high free T3 blood level;

(4) has no evidence of tissue thyrotoxicosis due to the high free T3 level, according to the results of serial ECGs, serum and urine biochemical tests, and bone densitometry.

Most of our euthyroid patients who improve or recover with metabolic rehabilitation involving T3 therapy meet these four criteria. Clearly, this set of findings in many treated euthyroid FMS patients shows that they meet Refetoff's definition of thyroid hormone resistance: "reduced responsiveness of target tissues to concentrations of thyroid hormone that under normal conditions would be excessive" (23). According to the four criteria, we have documented the presence of thyroid hormone resistance in FMS patients in several double-blind, placebo-controlled, crossover studies (27, 28, 31). Also, in a case-control study, we found that the results of the treatment lasted long term (29). Throughout a 1-to-5 year follow-up period, 10 hypothyroid FMS patients maintained their improvement compared to untreated FMS matched control patients. Also, 10 euthyroid FMS patients treated with T3 maintained their improvement compared to control patients.

Criticisms

Eisinger (rheumatologist) and Fontaine and Rinaldi (thyroid specialists) have given several criticisms of the hypothesis we present here (30). We agree with most of the criticisms. For example, we know that a small amount of the available evidence contradicts the hypothesis. Despite this, the hypothesis is supported by far more of the available evidence than is any competing hypothesis of the etiology of FMS. Also, rigorous logical analyses show that the hypothesis is the most useful at this time for stimulating further fruitful theoretical and experimental exploration of FMS.

Eisinger, Fontaine, and Rinaldi also argued that the hypothesis applies only to a subgroup of FMS patients. We maintain that the subgroup is large—close to 90%. We agree with them, however, that patients should be treated with precaution. We also agree with an astute observation of theirs: that when the peripheral cellular effects of thyroid hormone can be normalized by agents such as selenium (which may increase the monodeiodination of T4), this therapy is preferable to the use of exogenous thyroid hormone. (The American FMS/thyroid researcher Richard Garrison has made a similar argument.) We should rigorously study the treatment of FMS patients with agents such as thiol and selenium to learn whether some of the patients benefit more from these agents than from the use of T3. Even when patients do benefit from such agents, however, the benefits are mediated by an improvement in thyroid hormone regulation of cell function. This outcome further supports the hypothesis that in the involved patients, inadequate thyroid hormone regulation of cell function underlies their FMS.

Conclusions

If cellular resistance to thyroid hormone is accepted as a subset of thyroid disease not directly involving the thyroid gland, then our findings suggest that most FMS patients have thyroid disease. About 10% have laboratory test results consistent with primary hypothyroidism, and about 45% have results consistent with central hypothyroidism. This is a total of 55% of FMS patients who may have hypothyroidism.

Of the remaining 45% who have test results consistent with euthyroidism, 75% on average improve or recover when treated on the assumption that they have thyroid hormone resistance. This 75% is about 34% of our total sample of FMS patients. For a total percentage of FMS patients with possible thyroid disease, we can add this 34% of patients with thyroid hormone resistance (according to the four posttreatment criteria) to the 55% of hypothyroid patients (according to thyroid function test results). The result is 89% of FMS patients with putative thyroid disease. (See Table 1.)

This estimate is consistent with previous findings such as glycolysis abnormalities and T3-induced improvement in FMS patients with the polymyalgia-hypothyroid intractability syndrome described by Eisinger (11,14). In fact, as I (JCL) recently argued (11), virtually every symptom and abnormal finding in FMS is plausibly explained by inadequate thyroid hormone regulation. This proposed mechanism is unique in this respect.

Table 1. Percentage of FMS patients with thyroid disease.

Class of Thyroid Disease	**% of Patients**
Primary hypothyroid	10%
Central hypothyroid	45%
Thyroid hormone resistant	34%
Total % with thyroid disease	***89%***

The remaining 11% of FMS patients also have symptoms and signs that resemble those of hypothyroidism. Our conjecture is that these patients' symptoms and signs result from pathophysiological processes not related directly to thyroid hormone. However, we believe the pathophysiological processes in these patients impede metabolism in a set of tissues that generate symptoms and signs resembling those of hypothyroidism or thyroid hormone resistance.

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Follow-Up of Drs. Lowe's Trip to France.

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News from Dr. John C. Lowe

Metabolic Research and Educational Consulting — *March 8, 2010*
***The Metabolic Treatment of Fibromyalgia* by Dr. Lowe**

drlowe.com/contactus.htm (603) 391-6061 Tammy@drlowe.com

About Dr. Lowe Latest Updates to drlowe.com

If you're pregnant, you have an "in-range TSH level," yet you have high anti-thyroid antibodies, you are among women with a higher risk of losing your baby and sustaining harm yourself. Your doctor may reassure you that your high anti-thyroid antibodies aren't important because your TSH level is in range. If so, you should share with him or her the studies I include in the article below.

High Anti-thyroid Antibodies: Associated with Adverse Pregnancy Outcomes: *Even for Euthyroid Women*

Women often contact us to express a common concern. Their doctors have told them that their high anti-thyroid antibody levels are of no importance to their health. The women also tell us how their doctors justify this belief to them: "You're 'euthyroid,' the doctors explain. "That means your TSH is 'in range.' And when your TSH is in range, your thyroid function is just fine. So don't worry about the antibodies."

But two groups of women do remain concerned: those who have tried but can't get pregnant, and others who have had troubled or failed pregnancies. Both of these groups of women have science on their side: studies show that women who have in-range TSH and thyroid hormone levels but high anti-thyroid antibody levels are more likely to be infertile and to have complications of or failed pregnancies.

TO READ THE FULL ARTICLE

Pregnancy and Hyperthyroidism

Dr. R. Gärtner[1] wrote in 2009 that if a woman becomes overtly hyperthyroid during pregnancy, treatment with propylthiouracil (PTU) is proper. Indeed, last week, Dr. Rimpy Tandon and colleagues (in India) wrote in *Thyroid Science*[2] that PTU is commonly considered to be the safest drug for pregnant hyperthyroid women to use.

However, Dr. Tandon reported the case of a pregnant women under their care who took PTU.[2] The PTU induced hepatitis, and the woman lost her baby. During her second pregnancy, she developed hyperthyroidism again. During this pregnancy, Dr. Tandon treated her with a methimazole medication. This medication controlled her hyperthyroidism and enabled her to deliver a healthy baby. It appears, then, that methimazole drugs may be safer than PTU for some pregnant women. The full text of Dr. Tandon's report is available at no cost at *Thyroid Science*.

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McCain Bill Probably Dead!

My main article in this newsletter was to be a description of the McCain bill. Having read the bill, I know that in its present form, it would devastate the dietary supplement industry. It would also deprive us of many supplements we're now free to use. And it would send soaring the prices of most supplements that remain on the market.

We learned yesterday, however, that massive public protest caused Senator McCain to withdraw support for his own bill. At least in its original form, the bill is probably dead.

To me, McCain's bill is a display of the awesome power of Big Pharma over our legislators. In response to the bill, however, another awesome power has displayed itself: massive legislator-persuading protests from health care consumers. That McCain has reportedly backed down shows that our legislators listen when enough of us organize and vibrate the ears of Congress with the word "No!"

The apparent downfall of the McCain bill, in my opinion, is one more failed attempt by Big Pharma to recoup its losses to the natural health movement. It has lost plenty, and it will make move-after-move through our legislators and the FDA to recover its financial loses.

We appear to have won this time around. But a price we must pay for continuing freedom in our health care choices is to keep our noses in the air. Before long, the stench of Big Pharma's greed will waft down upon us again in the form of some legislator's bill. When it does, we must pay another price to keep our freedom: that is to organize once again and deliver a resounding "No!" to Congress.

To stay abreast of the unfolding events related to the McCain bill, see the website of the Alliance for Natural Health-USA: http://www.anh-usa.org/

Podcasts of Janie Bowthorpe Interviewing Dr. Lowe Available

Janie Bowthorpe of Stop-the-Thyroid-Madness interviewed Dr. John C. Lowe on January 7 and January 14, 2010. Janie provides recordings of the interviews. You can either listen or download the recordings. The recordings are available at the following website: http://www.talkshoe.com/talkshoe/web/talkCast.jsp?masterId=62603&cmd=tc

When you reach the page, look for "Episode 8" (1 hour 36 minutes) and "Episode 9" (2 hours 7 minutes). To download the recordings, click on the

München. roland.gaertner@med.uni-muenchen.de2.)

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Increased Need for Thyroid Hormone during Pregnancy

Dr. R. Gärtner[1] wrote that pregnancy increases the demand for thyroid hormone by 30%-to-50%. The thyroid gland, he added, has to cope with the increased demand for thyroid hormone. Because of the increased demand on the gland, he wrote that it's important that the pregnant woman get enough iodine, both during her pregnancy and when she's breast feeding.

Our Educational Services

Tammy Lowe

If you want to discuss the educational services we provide, please contact me. You can reach me by email at Tammy@drlowe.com or by phone at 603-391-6061. Our fax number is 303-496-6200.

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Archived Newsletters

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We also encourage you to listen to Janie's conversation with Dr. Kent Holtorf, recorded on February 17, 2010. The podcast of Dr. Holtorf is available on the same webpage as those of Dr. Lowe.

Janie Bowthorpe. Janie is like millions of other thyroid patients: she was kept ill on T4 replacement with Synthroid for years. Then she switched to Armour. Her recovery after escaping T4 replacement led to her becoming a valiant, enlivening, and rousing advocate of thyroid patients kept ill, as she was. She provides educational information and news for patients on her popular website, Stop-the-Thyroid-Madness.com. We encourage all thyroid patients to read Janie's book *Stop the Thyroid Madness*. Her story is inspiring, and she serves as a beacon for patients who are frustrated with their current medical care and want to know the path to improvement or recovery.

The Optimal Treatment for Hypothyroidism: John Lowe, DC

Dr. John Lowe Shares His Approach to Treating an Underactive Thyroid

By Mary Shomon, About.com Guide *Updated December 22, 2010*

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Discuss in the forum

One of the leading experts on hormonal health, Dr. John Lowe, has shared his thoughts about what constitutes optimal treatment for hypothyroidism, this series featuring practitioners with expertise in hormone balance and hypothyroidism diagnosis and treatment.

Dr. John Lowe believes that optimal treatment relies on careful evaluation, symptom management, and open-minded treatment.

John Lowe

In the course of successfully treating hypothyroidism (as well as most any other disease), Dr. John Lowe believes that relevant outcome measures are *crucial*. He says: "How else does the patient or clinician know with reasonable accuracy how well—or whether at all—the treatment regimen is working?"

According to Dr. Lowe, diagnosis comes first. In some venues, the clinician is limited in the number of blood tests he or she can order. This may be true, for example, in managed care or socialized medicine. When this is the case, he believes the clinician should order antithyroid antibodies.

Says Dr. Lowe:

> Endocrinologist Dr. Robert Volpé made this clear to me. He wrote that a patient may be hypothyroid due to antithyroid antibodies for a *few years* before the TSH rises and thyroid hormone levels decline. Among people who consume enough iodine, the most common cause of hypothyroidism is autoimmune thyroiditis. Because the TSH and thyroid hormone levels may reveal the hypothyroidism only years after a person develops autoimmune thyroiditis, the proper protocol is clear to me: test thyroid peroxidase and thyroglobulin antibody levels before concerning oneself with the TSH and thyroid hormone levels. If the clinician is free to order these latter tests, that's fine, but the antithyroid antibodies, to me, are far more important.
>
> However, as Dr. Bo Wikland has shown in *Thyroid Science*, many patients with hypothyroid symptoms caused by autoimmune thyroid disease *do not* have high antithyroid antibody levels. These patients may also have in-range TSH and thyroid hormone levels. Yet thyroid fine-needle aspiration shows that the patients' thyroid glands are festering with inflamed and antithyroid antibodies. Laboratory tests, then, including antithyroid antibodies, are *not* particularly reliable.

Dr. Lowe still believes that clinicians or patients should order the tests, but if the tests are all in range, he feels a patient shouldn't accept that he or she is negative for hypothyroidism. If the patient has symptoms and signs characteristic of hypothyroidism, he feels that a trial of thyroid hormone therapy is proper. According to Dr. Lowe, many patients, after beginning thyroid hormone therapy, recover from their symptoms and have a higher level of well-being. They improve despite never having had any lab test results that were consistent with hypothyroidism. For many patients, that is enough for them; they are satisfied with their treatment results.

According to Dr. Lowe, achieving optimal therapeutic results for many patients depends on them rejecting T4 replacement. Says Dr. Lowe:

> Instead of using that commercially-driven alternative, they should use one of the generally more effective alternatives. These include T4/T3 combination therapy (with either synthetic or natural thyroid hormones), or T3 alone. And they should ignore their TSH levels when searching for the dosages that are optimal for them—"optimal" in the sense of relieving their symptoms without overstimulation of their tissues. As I said, relief of symptoms and better well-being are sufficient for many patients. However, some patients get optimal results only when they also include physiological measures in their treatment regimen. I know some patients who obtain hand-held indirect calorimeters and actually measure their own basal metabolic rates. I know of no other physiological measurement that is more meaningful and useful. There are other relevant and useful measures, though, such as the basal body temperature, basal pulse rate, body weight, and perhaps the voltage of the R-wave on one's ECGs/EKGs.

In finding their safe and effective (optimal) thyroid hormone dosage, some patients use all of these physiological measures and they estimate of the intensity of their hypothyroid symptoms at close intervals to learn whether a particular thyroid hormone dosage is moving them in the right direction. And if they started out with high antithyroid antibody levels, they measure these again at intervals to ensure that their thyroid hormone therapy has acceptably lowered the levels. For Dr. Lowe, patients monitoring their responses to thyroid hormone therapy with these tools constitutes the best of outcome testing, which, in his experience, is more likely to provide patients with optimal treatment results.

Dr. John Lowe is a long-time thyroid and fibromyalgia researcher and practitioner, and Editor of the journal "Thyroid Science."

Dr. John Lowe's websites: www.drlowe.com, www.thyroidscience.com

Source: Email interview with John Lowe - December 2010

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reasons appear to be face saving. The reason I say this is that the policy that dominates other conventional medical specialities also dominates in pediatric care. That policy is "nothing risked, nothing gained," so assertively treat patients with drugs even when there is substantial evidence that they may harm them patients.

This policy, if applied to thyroid hormone therapy—which unlike most pharmaceutical therapies is harmless even when most patients' TSH levels are suppressed[6]—might have salvaged the infants' psychological functioning. But another factor the pediatricians didn't mention almost certainly caused them to use only the replacement approach—*despite them reporting that the infants remained psychologically impaired!*

That factor is the risk of brutal consequences for using a thyroid hormone therapy other than replacement. For clinicians in most parts of the world today to use doses of thyroid hormone higher than replacement doses risks punitive results that enforcer endocrinologists ensure medical regulatory boards will doll out to the clinicians. The risk of those dreaded consequences intimidates most clinicians into using only replacement doses. And the clinicians' compliance ensures that vast rivers of revenue continue to flow to Big Pharma from the sale of scores of millions of TSH assays.

Conclusion

A statistically significant percentage of the mothers and their newborns in the Swedish study suffered harm because T_4 replacement was ineffective for them. The harm to them may have been worse had the mothers had no thyroid hormone therapy at all. Then again, for some patients, T_4 replacement is little better than no treatment at all.
mothers and their newborns. This proof of har
from T_4 replacement would compel me to ask n
hypothyroid wife, were she pregnant, to gamble
another approach to thyroid hormone therapy. T
gynecologist feels the same way, and his wife w
soon see the local natural medicine doctor.

It's often hard for me to bear that adults a
commonly harmed by the ineffectiveness of T_4 r
placement. *But newborns, too?* In my firm opinio
subjecting newborns to harm by restricting th
hypothyroid mothers to T_4 replacement isn't jus
scientific and humanitarian issue; to me, it's also
moral one.

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Q: My wife had thyroid cancer 30 years ago and had her thyroid and parathyroid removed. Since then she has been on a daily dose of originally Armour, then later Synthroid. Can HSF replace those drugs? February 12, 2010

Dr. Lowe: I must apologize to you for a problem I have in answering your question forthrightly. The problem is that the FDA severely restricts free speech when it comes to products, such as HSF, classified as "dietary supplements," although many supplements (to speak obliquely) are powerfully health inducing. FDA restrictions dictate that we not relate a dietary supplement to any disease and that we not compare a supplement to a prescription drug. So much for our nation's founding fathers and their love of the open exchange of potentially-useful information.

However, the open access journal *Thyroid Science* (www.thyroidscience.com) has published two clinical trials in which I compared HSF to a synthetic T3 product. The T3 product, Cynomel, is a high-quality brand that US citizens can legally purchase from off-shore pharmacies without a prescription. That Cynomel isn't a prescription drug when purchased from an off-shore pharmacy enabled me (at some risk I suppose) to compare Cynomel to HSF. I'll refer you to those two studies so that you have access to the actual clinical testing of HSF.

Latest updates

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About Thyro-Gold^{TM}

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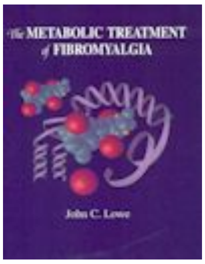
I am presently working with a laboratory to develop a dietary desiccated thyroid product that will be an improvement over HSF. It should be available in about six weeks. Unit-for-unit, it will be more health enhancing and less expensive than HSF. When the new product is available, Franconia Ltd, the company that owns www.ThyroidScience.us, will make it available at the website.

Again, I apologize for my FDA-zipped lips and the need to write indirectly about the question you asked. If you would prefer to communicate more directly and openly, I'm available for telephone consultations. Of course, we must charge for that service, which to me is a burden placed on health care consumers by FDA restrictions on free speech. But, alas, this is what the US in many ways has become—far too much like Joseph Stalin's USSR of the 1940s and 1950s.

All best wishes to your wife and you.



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Dr. John C. Lowe's

The Metabolic Treatment of Fibromyalgia

for Patients, Doctors, & Scientists

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E-Chapters
from Dr. John C. Lowe's
The Metabolic Treatment of Fibromyalgia

Table of Contents of the e-chapters is below on this page.

Dr. Lowe's *The Metabolic Treatment of Fibromyalgia* is an extraordinary book that has been widely and exceptionally acclaimed. For example, chemist Dr. Wayne D. Federer wrote:

> "John Lowe covers his subject with such scientific rigor, breadth, and cohesiveness as one seldom if ever finds in medical texts of any type, let alone low-budget 'alternative' ones. Its excellent readability and accessible organization; its rich mining and critical analysis of the literature pertaining to all aspects of metabolism, from earlier generations to present day; and its highly creative and interdisciplinary presentation of 'the big picture' are all qualities that assure this book a prominent place on my shelf for a long time. On thyroidology, I would not hesitate to compare this book to authoritative multi-author references such as *Werner & Ingbar's The Thyroid* or *The Thyroid and Its Diseases."*

Similarly, Dr. Mark Swanson, naturopathic physician and former Associate Editor of the *Journal of Naturopathic Medicine,* wrote:

> "An outstanding contribution that transcends the boundaries of medicine . . . comprehensive in every detail, remarkable, and brilliantly written. This is an exhaustive work that provides powerful evidence linking cellular hypometabolism from inadequate thyroid hormone regulation to the cause of fibromyalgia. I am awestruck at Dr. Lowe's authoritative and in depth understanding of this subject. For patients who are fortunate enough to be treated by the protocols outlined in the book, this will come as a very special gift."

We'll end the quotes with these two, although we could publish a moderate-size book filled with the words of praise we have received from readers of the book.

We will point out, however, that in Dr. Lowe's large Chapter 1.2 (Fibromyalgia is Not a "Somatoform Disorder)**,** he so eloquently and resoundingly debunks the belief that fibromyalgia is a psychiatric disorder that Study Sphere gave it the Award of Excellence.

So extraordinary is *The Metabolic Treatment of Fibromyalgia* that the world's largest medical/health publishing corporation, Elsevier Ltd, has tried numerous times to obtain the rights to publish *The Metabolic Treatment of Fibromyalgia.* We are happy to report, however, that Dr. Lowe has declined Elsevier and continued our publishing relationship. We are proud to continue making the book available, and at a far lower price than Elsevier would charge.

E-Chapters. Many people who purchased the hardback book have asked us to provide a CD or e-chapters of the book. We finally have done so. Below is a table of contents of the e-chapters.

Most of the chapters in the book are very large. Below, under each chapter name, we give the page and word count of the chapter. We did this to let you know the amount of information contained in the chapter. Other books on hypothyroidism and fibromyalgia that we have in our shelves average about 50,000 words.

We would like to emphasize that *The Metabolic Treatment of Fibromyalgia* is not only about fibromyalgia. Dr. Lowe uses fibromyalgia as pattern of symptoms and signs to illustrate what he terms "inadequate thyroid hormone regulation of cell function." But in the book, he comprehensively covers practically every aspect of the basic and clinical sciences of thyroidology. As Dr. Feberer wrote, he "would not hesitate to compare this book to authoritative multi-author references such as *Werner & Ingbar's The Thyroid* or *The Thyroid and Its Diseases."* What your have below, then, is a truly exceptional book, chapter-by-chapter, that covers most of two fields, fibromyalgia and thyroidology.

The pages in *The Metabolic Treatment of Fibromyalgia* are 8½ x 11 inches.

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Thank you for your interest in the chapters in Dr. John C. Lowe's
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Appendix A

- Fibromyalgia Assessment Forms, Blank Line Graphs & Scoring Instructions, and Conversions: T_4, T_3, and Desiccated Thyroid . . . .

22 pages

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Appendix B *(Appendix B is not yet completed.)*

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Thyro-Gold has 300 mg of thyroid powder in each capsule. Do you know why other products have only 130 mg per capsule?

November 30, 2009

Q: I'm happy to find that Thyro-Gold is a dietary thyroid supplements and doesn't require a prescription. I've ordered it already. I'll be grateful if you'll answer a question for me. I notice that a Thyro-Gold capsule has 300 mg of thyroid powder in it. Why do most other over-the-counter desiccated thyroid products have only 130 mg dosage?

Dr. Lowe: I don't know for sure. My assumption is that people who used dietary desiccated thyroid powder in the past came to 130 mg of powder per capsule through trial and error.

Several years ago, I talked with a gentleman who started a well-known company that markets a dietary desiccated thyroid product that contains 130 mg of powder per capsule. He told me he had taken the time to talk with customers who repeatedly bought the product. Of those who said they had recovered their health, he asked how many capsules did the job for them. On average, he said, customers were satisfied with their use of the product when they took either 6, 7, or 8 capsules each day. The range of satisfactory daily dosages, then, was 6-to-8 capsules.

If he was correct about the dosage range that satisfied most customers, it means this: There were three sets of customers: (1) those who did well taking 780 mg of powder, (2) others who did well with 910 mg, and (3) others who needed to take 1040 mg.

Latest updates

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About Thyro-Gold^{TM}

Let's say that those customers want to switch from the other product to Thyro-Gold. To get the same amount of thyroid powder with Thyro-Gold, customers who take 6 capsules of the other product will take only 2.6 capsules of Thyro-Gold. Those who take 7 capsules of the other product will take 3 Thyro-Gold capsules. And those who take 8 capsules of the other product will take only 3.5 capsules of Thyro-Gold.

You may wonder about taking half of a capsule of Thyro-Gold, or a little more or less. One can easily pull open Thyro-Gold capsules and then portion out the powder however he or she wants. I hope this is helpful to you, and I wish you the best with your use of Thyro-Gold.

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| Letters Related to Dr. Lowe's Rebuttal to British Thyroid Association |

Subject: Are euthyroid patients harmed by thyroxine therapy
Date: June 20, 2010
From: Author prefers anonymity
To: editor@thyroidscience.com

June 20, 2010
Question: I am a general practitioner in the UK. Many of my patients have told me that they recovered from their hypothyroid symptoms after they found a private doctor who treated them with thyroxine despite their normal TSH levels. These patients had been denied thyroxine treatment by doctors within the National Health Service because of their normal TSH levels. So many patients have told me this that I have developed reservations about ruling out hypothyroidism and the need for thyroxine therapy based on a normal TSH test.

Many more of my patients with normal TSH levels ask me to prescribe thyroxine or Armour Thyroid. I am hesitant to comply because of the Royal College of Physicians' statement about adverse effects from unnecessary thyroid hormone therapy. May I have your point of view on the potential for adverse effects from thyroxine treatment when patients do not actually need it?

Dr. Lowe: I'm familiar with the statement you refer to by the Royal College of Physicians. Specifically it is: ". . . some patients are inappropriately diagnosed as being hypothyroid (often outside the NHS) and are started on thyroxine or other thyroid hormones ***which will not only cause them possible harm*** . . ." (Italics and bold mine.)

Like too many other statements or implications by the Royal College of Physicians, when applied to the general population, this one is *patently false.*

Unless you're a geriatric specialist whose patients are among the most fragile of human beings, even if they don't need supplemental thyroid hormone, a trial of thyroid hormone therapy is harmless. If the hormone doesn't help them, you can wean them off it and then have them stop it altogether. *No harm done!*

Proof of this is in the history of FDA-guided studies of the potency and stability of T4. To test T4 for potency and stability, researchers—*using FDA test guidance!*—have *traditionally* used volunteers who were "euthyroid," meaning, of course, that they subjects had normal thyroid function test results. Moreover, FDA test guidance has allowed researchers to use euthyroid volunteers to test higher-than-physiological (supraphysiologic) doses of T4.[1,p.109]

I ask the Royal College of Physicians: If it were likely to harm euthyroid volunteers, why would FDA-test guidance allow researchers to use them for the testing? And why would institutional review boards approve the studies as *not potentially harmful* to the volunteers?

The answer is simple, of course: A trial of thyroid hormone therapy—even for people with perfectly normal thyroid function—is *harmless*, even when they use *supraphysiologic* doses.

Only recently have researchers suggested that rather than testing euthyroid volunteers, they would best use thyroidectomized patients. But the researchers' reason for this suggestion has *nothing whatever* to do with any harm ever done to euthyroid volunteers in the studies. The testing hasn't harmed the euthyroid volunteers, nor will a trial of thyroid hormone therapy harm practically any of your euthyroid patients except possibly the most severely fragile of them. But, then, a cup of coffee is just as likely to harm those fragile folks.

I just don't understand something: How does the Royal College of Physicians (as with this particular issue) and the British Thyroid Association make scientifically false statements and stand by them in the face of proof that they are false, yet receive no official reprimands from regulatory authorities in the UK? To me, their false statements are an affront to the noble tradition of science, and the organizations sticking by their false statements in the face of refuting evidence reduces the statements to examples of pseudoscience.

At any rate, I hope this reply is helpful to you in providing your patients with harmless trials of thyroid hormone therapy, whether they truly need it or not.

Reference

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(This Q&A was published simultaneously at drlowe.com)

Letter to the Editor

Subject: Question about where to submit my paper
Date: June 12, 2010
From: Author prefers anonymity
To: editor@thyroidscience.com

June 12, 2010

Question: I have a hypothesis paper that I'm considering submitting to *Thyroid Science*. I'm hesitant, however, because there may be advantages to publishing in major medical journals, such as the *Journal of the American Medical Association*. Of course, I may have a harder time getting my paper accepted because of competition. What are your thoughts for people who are new to submitting papers to journals? Can I submit my paper both to *Thyroid Science* and another journal and go with which ever journal accept it?

Dr. Lowe: Many people have asked us this same question. Of course, we would like a chance to publish your paper if our reviewers believe it has merit in the field of thyroidology. However, if your paper may contribute to changing the current "T4 replacement paradigm" for hypothyroidism, we really don't care which journal first publishes it, as long as you get it published.

To some, that policy may seem self-sabotaging to *Thyroid Science,* but it really isn't. If we feel that a paper published elsewhere is important enough, we'll ask the author(s) to write a summary of the paper for our journal, possibly further articulating the thesis and providing more supporting evidence. And if the author won't cooperate, we may compose a paper based on the author(s)' that provides the important information for our readers.

In deciding where to submit your paper, you might keep in mind a few points I wrote to another potential author this morning. What I wrote to him is essentially the following.

Long ago, when I was being educated in research psychology (I think Galileo sat two rows in front of me), I took courses that dealt with the ethics of scientific conduct. We were taught that it's unethical to publish exactly the same paper in more than one journal, even if years have passed since the first publication. That policy is an old one, and it still applies. Because of this, you should submit your paper only to one journal at a time. If the first journal rejects your paper, then, and only then, submit it to the next one.

If you want to spread your hypothesis wider than one journal would allow, you can easily do that. First, publish your paper in one journal, and write as many other papers as you want for other journals. This is perfectly ethical as long as your other versions of your paper are indeed other versions; that is, in subsequent papers, you should express your hypothesis exactly as it was originally published, but *in different terms*. Expressing the same thoughts in different terms is ethical. In my view, in fact, if you feel that your hypothesis can lead to the relief of suffering of human beings, you have a humanitarian responsibility to publish it as many times as needed to accomplish that worthy end.

If you can get your paper accepted by a major traditional print journal, you'll have some important advantages. For example, you're likely to have more prestige in the eyes of the typical practicing conventional clinician, and your paper will be included in the traditional major indexing systems, such as Medline.

On the other hand, the print journal may fail to publish your paper in an open-access electronic version of the journal. If so, only those who subscribe to the print version of the journal are likely to read your full paper. As time passes, the only part of your paper that most interested people will have access to will be the abstract that is online. They can access your abstract through most search engines, such as Google and Yahoo.

Otherwise, if anyone is interested enough in arrange to get a copy of your full paper, he or she will have one of two options: First, he or she can buy a copy online from the closed-access journal. This can be expensive, and it can be prohibitive if one does a great deal of journal research. Second, he or she can travel to a medical library, track down your paper in a bound volume of all the papers published in that journal during the year, and photocopy it. This option is inconvenient for most people. This may account for me seeing in recent years fewer and fewer people in medical libraries copying journal papers.

Another downside of traditional print journals is something that frustrated many of us who used to publish in traditional print journals: the “publication lag.” I know of some journals that had a lag of two years. This meant that by the time one’s paper was published, it was more history than news. Because of the publication lag, I encourage you talk or write to an editor of the journal you decide to submit to. As whether in addition to publishing a print version, the journal will also rapidly publish an electronic version online.

Another important issue is whether the journal is available only to subscribers ("closed-access") or is "open-access." Open-access means that most publications in the journal are free to read without a subscription. Steadily more open-access journals are being published, and they are impacting traditional print journals. When I've inquired, medical librarians, who work where traditional print journals are stored, have told me, “open-access journals are killing us.”

One advantage of electronic publishing, especially in open-access journals such as *Thyroid Science*, is that we have virtually no publication lag. We publish papers are rapidly compared to print journals. In addition, with open-access journals, anyone in the world with access to the Internet can find and read your paper using Google, Yahoo, or most any other search engines. One doesn't even need to use Medline, PubMed, or any of the other traditional indexing system. In fact, I believe these systems are on the verge of being obsolete. Most search engines such as Google also index the papers that formerly were indexed only in the traditional indexing systems. Plus, Internet search engines also indexe publications *not* included in PubMed.

If you publish in another journal for whatever advantage, we fully support you in it. And if you'll send us an advanced copy of your paper, after the other journal publishes it, we may ask you to summarize your hypothesis and elaborate on it in a second paper for *Thyroid Science*.

Best of luck in getting your hypothesis published, wherever you decide to submit your paper.

Letter to the Editor

Subject: What is prealbumin
Date: November 24, 2009
From: Author prefers anonymity
To: editor@thyroidscience.com

My doctor gave me my lab results yesterday. I know what most of the thyroid tests are, but I've never heard of one. It is the "prealbumin." Do you know what this is? My level was 0.20 g/L, and the range is listed as 0.18-to-0.39 g/L. Do you know what this result means?

Reply by Dr. John C. Lowe, Editor-in-Chief (November 24, 2009)

Dear Bob: We have a newer name for prealbumin, which is "transthyretin." Transthyretin is a protein that is important to thyroid hormone regulation of the brain. The protein transports thyroid hormone across the blood-brain barrier; that is, from the blood outside the brain to the blood inside brain. Transthyretin that transports thyroid hormone in the blood is produced in the liver, but transthyretin that transports thyroid hormone across the blood brain barrier is produced in a structure called the "choroid plexus" at the base of the brain.

When I say that the protein transports thyroid hormone across the blood-brain barrier, I mean that it transports both T4 and T3. This is important to understand. The reason is that many clinicians mistakenly think that transthyretin transports only T4 into the brain. Based on this mistaken belief, these clinicians also mistakenly believe that normal brain function depends on patients including T4 in their thyroid hormone therapy. This, however, is patently false. (Elsewhere, I extensively documented that transthyretin transports both T4 and T3 into the brain. I published one article in 2005 and the second in 2006.)

You wrote that your transthyretin level was 0.20 g/L (20 mg/dL). With a range of 0.18-to-0.39 g/L (18-to-39 mg/dL), your level is very low; it's in the lower 4th of the range.

Some diagnosticians would say this level means you're not producing an optimal amount of transthyretin; others would say that you're producing plenty. I don't think we have enough studies to tell us which of those diagnosticians are right and wrong.

What we can tell from your level is that you're producing the protein and your most likely getting thyroid hormone into your brain. We don't have tests commercially available that measure the amount of thyroid hormone that is bound to one's transthyretin. That piece of information would be valuable. The reason is that dioxins and PCBs can displace thyroid hormone from the protein. As a result, these chemical contaminants can ride into the brain on the protein. The more of the contaminants that ride the protein into the brain, the less T4 and T3 are likely to reach brain cells. Once inside the brain, dioxins and PCBs bind to T3 receptors on genes. The binding alters the pattern of codes that the genes send out to the work part of the cell for the production of proteins. I believe this phenomenon is responsible for some of the cognitive and mood problems of people contaminated with dioxins and PCBs, which toxicologists have told me is each of us. (I heavily documented the thyroid-disrupting effects of these pollutants in the "Environmental Contaminants" section in Chapter 2.4, "Thyroid Hormone Deficiency," of *The Metabolic Treatment of Fibromyalgia* [available in the publisher's E-Chapter section].)

I assume that you wrote to me about your transthyretin level from concern about your thyroid hormone status. However, some clinicians order the test to learn whether a patient is ingesting enough protein. Transthyretin is a "glycoprotein," which means it is a carbohydrate combined with a protein. Of all the proteins in the blood, it's transthyretin that is most useful in telling whether a person has a protein deficiency. The half life of the protein is about two days, so it's level in the blood changes quickly when someone markedly decreases or increases protein intake, digestion, and/or absorption.

You didn't say whether you ate little to no protein for several days before your blood was drawn to measure your transthyretin. If you ate little to none, that might account for your low-range transthyretin level. If that is the case, you should talk with your clinician about measuring your transthyretin level again after you eat 50-to-75 grams of protein each day for several days. Your tranthyretin level might then be higher. But keep in mind that inflammation and infection can also lower transthyretin level, and severe kidney disease and the use of glucocorticoid (such as prednisone or prednisolone) can raise your level. I hope this is helpful to you.

Letter to the Editor

Subject: Followup photo of goiter patient
From: Ned Fuller
Date: March 1, 2009 10:08 am
To: editor@thyroidscience.com

My mother has a goiter and it has been advised that she have it surgically reduced. I am a physician but have not had the opportunity to see the postsurgical appearance of the neck after a patient's goiter has been removed. My mother is concerned about the appearance, although she is also concerned about the appearance of the goiter. Are there any postsurgical photos of the patient whose goiter Drs. De Sousa, Dilip, Mervyn removed.

Editor's Reply (March 2, 2009)

Dear Dr. Roberts: We asked Dr. DeSousa if any photos were available of the patient whose goiter he and his colleagues reported removing. He was kind enough to send the postoperation photo to the right below. We also posted below the photo of the patient from the authors' case report before they removed the goiter; it is the photo to the left.

Dr. De Sousa wrote to us that the photo to the right is the patient after two weeks of convalescence. The scar had been painted with mercurochrome. We are grateful to Dr. De Sousa for providing *Thyroid Science* with the photos, and I hope the postop photo is helpful to you, Dr. Roberts.

Tracy Majors
Assistant Editor

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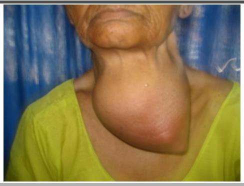

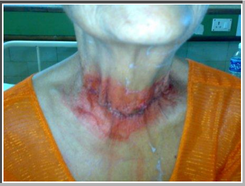

Letter to the Editor

Subject: Thanks to you!
From: Jacqueline Herrera
Date: Mon, December 8, 2008 9:32 pm
To: editor@thyroidscience.com

Dear Dr. Lowe: I'm so thankful I was told about ThyroidScience.com. I read the article on "Weight Gain and the TSH" and sent it to my three sisters who also suffer from hypothyroidism. I started the Armour Thyroid medication almost two weeks ago and feel so much better than the last 7 years of being on levothyroxine. I know this is a positive start in the right direction for me personally. I have 30 pounds to get rid of that I've gained in the last 7 years after two consecutive pregnancies in 2002 and 2003. Thank you for making this information available to the people (not just doctors) who are pro active about their health.

Jacqueline Herrera
Phoenix, Arizona

Editor's Reply (December 25, 2008)

Dear Jacqueline: Thanks so much for writing about feeling better on Armour Thyroid after gaining thirty pounds of weight while on levothyroxine. If you use a high enough dosage of Armour, I expect that you'll lose the 30 lbs you gained over the seven years that you used levothyroxine. This is especially likely if you have a wholesome diet and regularly exercise to tolerance.

Armour Thyroid, like Nature-Throid and Westhroid, is more effective than levothyroxine at reducing body fat. The reason is that these products contain T3. Some researchers say that T3 has a "lipolytic"—that is, a fat-decomposing—action in fat cells.[3] One way T3 reduces fat in the cells is by inhibiting an enzyme (cyclic-AMP phosphodiesterase) that slows down metabolism shortly after adrenaline and noradrenaline speeds it up.[1][3][8] By blocking this enzyme, T3 sustains the fat-decomposing effect of adrenaline and noradrenaline in fat cells.[1][2][8] Another way T3 reduces fat is by altering gene transcription for several compounds. When T3, acting through the relevant genes, increases fat cells' production of these compounds, the compounds augment adrenaline's and noradrenaline's fat-lowering effect in the cells.[10]

In addition to weight loss, you may get another benefit from the T3 in Armour: that is, a reduction of fat that probably accumulated in your arteries[3] while you were on T4 replacement. As Duntas wrote,[11] As Duntas noted in 2002, the composition and transport of blood fats "are seriously disturbed in thyroid diseases." Among patients with an high TSH and low thyroid hormone levels, cholesterol and LDL are typically high. Even when thyroid hormone levels are within the reference range but the TSH is high, patients on average have a slightly high total cholesterol, high LDL, and low HDL. These patients also have abnormalities of the linings of arteries, inflammation and fat accumulation in the aorta, and they are subject to have myocardial infarctions. They also have increased resistance to blood flow, weaker contractions of the heart muscle, and increase diastolic blood pressure. As Duntas pointed out, thyroid hormone therapy—*especially with TSH-suppressive dosages*—"usually leads to a considerable improvement in the lipid profile."

T3 reduces fat in artery linings in part by increasing the activity of an enzyme called "lipoprotein lipase."[4] Low activity of this enzyme leads to high blood fats, which is a risk factor for coronary heart disease.[7] Thyroid hormone increases the activity of the enzyme, and by doing so, it reduces blood fats.[4] Thyroid hormone also lowers LDL cholesterol by increasing the number of LDL receptors on liver cells.[11]

In my clinical experience, thyroid hormone therapy (with products that contain T3) is by far more effective than statin drugs in normalizing blood fats. I believe that if patients in general were allowed to use effective thyroid hormone therapy rather than T4 replacement, we could virtually eliminate the market for statin drugs. Then patients would be free from the potential adverse effects of statin drugs, such as chronic muscle pain and other pain syndromes, elevated liver enzymes, peripheral neuropathy, and muscle damage.[9]

Please let us know how you progress. I wish you the best for losing the weight you gained while on levothyroxine.

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Letter to the Editor

From: "Lars" <staff@bicom.se>
Date: Sun, November 16, 2008 2:06 am
To: Editor@thyroidscience.com

Has the paper below really been reviewed????

http://www.thyroidscience.com/studies/overbye.2007/overbye.metabolicfailure.fms.lowethesis.pdf

I do not question the Lowe thesis, but I believe that a poor paper to support it is in fact harming the cause—especially if the methods used are not backed up with known or accepted methods.

Kind regards
Lars Németh
Med Vänlig hälsning
+46 40 137 765

Editor's Reply

Dear Mr. Németh: Thank you for your email and your thoughts. Yes, indeed: Dr. Øverbye's paper was reviewed. Several of our peer reviewers read the paper, and each strongly recommended that we publish it. As one of the reviewers commented after critiquing Dr. Øverbye's manuscript, "This paper reports the type of cutting-edge, creative pilot research that we want to encourage."

You suggest that Dr. Øverbye's paper is "poor" because his methods were "not backed up with known or accepted methods." In conventional medicine, of course, creative research using innovative methods has traditionally been resoundingly discouraged. Recall the dictum, "Be not the first by whom the new is tried, nor the last to lay the old aside." We at *Thyroid Science* reject this progress-stifling, herd-mentality orientation. Instead, we encourage originative and progressive clinical methods and research. That orientation is exemplified by *Thyroid Science* publishing Dr. Øverbye's paper. As objectionable as this orientation may be to some people within conventional medicine, we steadfastly stand by it, as we believe this orientation is likely to bring help to millions of thyroid patients whom conventional medicine continues to fail.

Your assessment of Dr. Øverbye's study and his paper brings to mind similar notable occurrences. They involved Professor Linus Pauling, a two-time Nobel Prize winner ranked among the ten most fruitful scientists in history. Pauling was also fruitful in his scientific investigations in the field of nutrition. But editors of medical journals often censored him by rejecting or delaying publication of his manuscripts because the contents challenged conventional medical prejudices. (To read his description of the censorship by editors—including the editor of the *Journal of the American Medical Association*—read his chapter titled "Organized Medicine and the Vitamins" in his book for the public titled *How to Live Longer And Feel Better*.)

By contrast, after some resistance early in his career, chemistry journals accepted Pauling's thinking and methods that were clearly beyond the boundaries of "the box." Some editors accepted his manuscripts containing extremely innovative material without sending them to peer reviewers. As one editor noted, peer reviews were impossible in that Pauling had no peers. The chemistry profession got the benefit of Pauling's imaginative and innovative mind. But censorship of this scientific genius protected from refutation the presumptions and prejudices of the editors, commercial sponsors, and readers of some medical journals.

I'm not saying that Dr. Øverbye's paper is certain to have the gargantuan scientific importance of many of Pauling's papers (although I'm also not saying it won't). What I am saying is that *Thyroid Science* will not censor research simply because it involves thoughtful, fresh ideas, and innovative methods. As in Dr.

Øverbye's case, we encourage researchers to use well-established technologies from other fields to make scientific advancements in the field of medicine. He has done this, and admirably so.

We appreciate you expressing your opinion and prompting us to explain why our reviewers and editors enthusiastically accepted Dr. Øverbye's paper for publication.

Best wishes,
Dr. John C. Lowe
Editor-in-Chief
Thyroid Science (Editor@ThyroidScience.com)

Letter to the Editor

Subject: Thyroid Weight Gain
From: June Hyslop <Scotland, UK>
Date: Sun, November 16, 2008 6:34 am
To: editor@thyroidscience.com

Dear Dr. Lowe: I am printing off a copy of your article "Weight Gain and the TSH: Prevention Writer's Good Deed." I will take it to my next appointment with my endocrinologist in the hope that he'll read it and adopt a less conservative approach to the management of my hypothyroidism. At my last visit he cut my thyroid medication because I was too near the top of the range for FT3 and FT4 (my TSH is suppressed already). It's now two months later and I have gained five pounds. As I was already overweight and have extreme difficulty losing any, this is a big setback for me. I'm also fatigued and have seen the return of other hypothyroid symptoms since the reduction in dose.

I feel there is a lack of understanding within the endocrinology community about how this affects patients physically and mentally, and I would like to see a more open-minded and individualized approach to patient management. Your efforts in this regard are greatly appreciated, and I look forward to receiving future issues of *Thyroid Science*.

June Hyslop
Scotland, UK

Editor's Reply

Dear June: Thank you for your email. Since we published the editorial on weight gain and the TSH, we've received many emails from hypothyroid patients expressing the same lament that you do. Over the years, I've heard so many patients express the same grief that I couldn't begin to count them. Your complaint about weight gain and those of many others, and the studies I cited in the editorial, make one point clear: basing hypothyroid patients' treatment on their TSH levels (or their thyroid hormone levels) is an egregious wrong imposed on the patients. Indeed, that approach is the very cause of many patients gaining weight that they can't lose despite regular exercise and a wholesome, nonfattening diet.

One way to rectify this wrong in medical care is exactly what you've said you'll do—put the evidence of its harm, shown in studies, before the eyes of endocrinologists and other practitioners. Patients must, of course, insist that the clinicians pay attention to the studies and rationally consider them. Of course, it's now legend that many endocrinologists rudely dismiss patients who bring to their attention scientific evidence that contradicts their beliefs. The patient who accepts the dismissal and finds a more scientifically-thinking clinician is fortunate; he or she is far more likely to receive safe and effective care.

According to case law in the U.S., clinicians have a professional responsibility to stay abreast of scientific evidence that bears on the opinions they give their patients. So for an endocrinologist to deny to a patient that weight gain is associated with in-range rising TSH levels is—by virtue of the available scientific evidence—a breach of professional responsibility. But this is a breech that many endocrinologists sidestep. They do so by deferring to the practice guidelines written by committees within their specialty. The practice guidelines dictate standards for the diagnosis and treatment of hypothyroidism both within the endocrinology specialty and, by extension, in other medical specialties. Largely under the sway of corporations' financial inducements, too many of the members of these committees ignore the scientific evidence that shows the potential harm from parts of their guidelines that favor corporate profits. (I heavily document these potential harms throughout *The Metabolic Treatment of Fibromyalgia*.) In essence, then, these committees nullify the practicing endocrinologists' responsibility to listen and learn when patients troubled by weight gain give them the scientific evidence that the gain is associated with TSH levels within the reference range.

This harmful system within the endocrinology specialty has alienated countless hypothyroid patients who now hold the specialty in contempt. I believe this is a good dynamic because of a phenomenon in the 20th century history of medicine in the U.S. That phenomenon was that major changes in medicine came about because enough patients demanded them and made them profitable. The patients sought out and paid clinicians who provided services they wanted. Many of those patients wanted the services because they, unlike the clinicians, knew of scientific evidence that the services could benefit them. This market demand was a major influence on the emergence of sports medicine, nutritional medicine, integrative medicine, and manual manipulation by medical practitioners. Scientific evidence favoring these methods had long existed. It received little-to-no attention by physicians, however, until patients made it profitable for them to provide the services warranted by the evidence.

Will the endocrinology specialty overall yield to mass patient demand? Not until that huge barricade of corporate money is ceases to wall off the minds of most endocrinologists from the scientific evidence. Removing that barricade will be a difficult task indeed in this world where corporatism overwhelmingly prevails.

Over the last several years, however, I've seen signs that a minority of endocrinologists have come around. If patients like you seek out and patronize those endocrinologists, their numbers are likely to grow. I encourage you, then, to put the editorial on weight gain and the TSH before your endocrinologist's eyes. (I recommend that you print the pdf version of the editorial, which you can download or print at no cost.) If you are rebuffed in your attempt to enlighten him, I hope you'll move on and find one within that minority of endocrinologists who'll give you better quality care by ignoring the levels of your TSH and thyroid hormones in deciding what dosage is best for you.

Yours sincerely,
Sincerely,
Dr. John C. Lowe
Editor-in-Chief
Thyroid Science (Editor@ThyroidScience.com)

Subject: Re: Doing better on Armour
From: Anonymous patient in Australia
Date: Wed, August 27, 2008 6:11 pm
To: editor@thyroidscience.com

Dear Editors: I bow down to you as I read everything you publish on thyroid. Please keep it up. After using thyroxine, I now use Armour and finally feel better.

Dear Reader: The next Q&A down from this one is a question from a physician and an answer to it by Dr. John C. Lowe, our Editor-in-Chief. As his answer indicates, we at *Thyroid Science* are aware of the superiority of desiccated thyroid products, such as Armour, Nature-Thyroid, and Westhroid, over thyroxine (T4) alone. You may find very interesting an article we will soon publish. It is a rebuttal by Dr. Lowe to the British Thyroid Association's denouncement of desiccated thyroid products. We will send an email notice to our subscribers when we publish the rebuttal. We appreciate you letting us know that you are doing better on desiccated thyroid.

Sincerely,
Tracy Majors
Assistant Editor
Thyroid Science (www.ThyroidScience.com)

Subject: **Safety Precautions for Thyroid Hormone Therapy**
From: Anonymous physician
Date: Thu, August 24, 2008 12:29 pm
To: Editor@thyroidscience.com

Dear Dr. Lowe: I am one of the many family physicians who has jumped off the ship of conventional medicine and onto that of natural medicine. I spent my first twenty years of practice disserving my thyroid patients by prescribing Synthroid only and changing their dosages by their TSH levels. It didn't take much experience for me to see that products like Nature-Thyroid work better than Synthroid with most patients, especially when I ignore their TSH (as you give evidence for doing in your critique of T4 vs T4/T3 studies) and go by their symptoms, temperature, Achilles reflex, and physical appearance. I read in your book *The Metabolic Treatment of Fibromyalgia* about the change in some patients' eyes and general appearance when they switch from T4 to desiccated thyroid or T3. When I use these meds correctly, they almost always seem to turn up the patient's rheostat, whereas usually Synthroid just left it turned off. I feel bad that I spent so many years neglecting to treat patients better with thyroid hormone, but that is what I was taught in medical school. I know you're big on treating underlying conditions that can interfere with thyroid patients responding well to thyroid therapy. Not wanting to harm my patients any more than I did over the last twenty years, can you brief me on the scope of underlying conditions I should look for. If you post my email, please do it anonymously. I have been cautioned that a low profile is best for keeping my license to practice medicine.

Dear Doctor: Welcome to the rational, scientific side of clinical thyroidology. I don't know what caused you to jump ship from conventional (to me, commercial) medicine, but I'm pleased that you're sailing with us now.

Precautions, of course, are steps we take to avert harming the patients we treat with thyroid hormone. We take most of the steps in advance of the patient beginning thyroid hormone therapy. But we must take some steps, as I explain below, after the patient has begun treatment.

The precautions I take involve the following steps: (1) ensuring the cardiac safety of the patient, (2) learning his or her cortisol status, (3) determining whether he or she has blood sugar dysregulation, (4) making sure he or she both exercises regularly and (5) takes a wide array of nutritional supplements.

A company (Erfa Canada, Inc.) that markets a brand of desiccated thyroid gives an overview of prudent precautions with thyroid hormone therapy. The company's precautions are important. I recommend additional ones, but their precautions are worth quoting.

Patient' Cardiovascular Status: The company recommends: "Thyroid hormones should be used with great caution in a number of circumstances where the integrity of the cardiovascular system, particularly the coronary arteries, is suspect. These include patients with angina pectoris, hypertension, other cardiac conditions, or the elderly, in whom there is a greater likelihood of occult cardiac disease."

Some doctors unfortunately deny patients with delicate cardiovascular conditions any use of thyroid hormone. This is unfortunate because many of these patients can safely use and benefit from thyroid hormone; in fact, many cardiac patients must use thyroid hormone therapy to recover cardiac health.

Caution is the key to guiding these patients back to a healthy heart. The Erfa website describes a precautionary treatment approach: "In these patients, therapy should be initiated with low doses, i.e., 25 to 50 μg levothyroxine (T4) or its isocaloric equivalent (16 to 32 mg, or 0.25 to 0.5 grain of desiccated thyroid).

When, in such patients, a euthyroid state can only be reached at the expense of an aggravation of the cardiovascular disease, thyroid hormone dosage should be *reduced*." (Italics mine.)

I agree with this cautious approach except for two things. First, the company mentioned the patient reaching a euthyroid state. This implies using a thyroid hormone dosage that keeps the TSH, free T4, and free T3 within their reference ranges. Bringing these hormones into their reference ranges, however, does *not* render most patients well. At its website, Erfa tells what does: "The principal pharmacologic effect of exogenous thyroid hormones is to increase the metabolic rate of body tissues." The safest and most efficient way to help patients get well is to free them from their symptoms by normalizing their metabolic rates. Hence, rather than a *euthyroid* state, we should instead strive for a *eumetabolic* state.

What I next disagree with is the company's advice that some cardiac patients start treatment with a T4 product. These products may not work at all for many cardiac patients, regardless of the dosages they use. If the patient is hypothyroid, I recommend a T4/T3 product with a T4 to T3 ratio of 4:1, or T3 alone. Some T4/T3 products with the proper ratio are Armour Thyroid, Nature-Thyroid, and Westhroid. I prefer the latter two products for two reasons. First, an occasional patient reports to me that when she takes Armour, she develops itching, which I assume is an allergic reaction. Switching to Nature-Throid or Westhroid relieves the itching. Second, the manufacturer of Nature-Throid and Westhroid, RLC Labs, goes to great lengths to ensure the quality, safety, and evidential basis of their therapeutic products. This is obvious in their description of how they formulate a variety of therapeutic products.

I always do an electrocardiogram (ECG) when I see patients personally. If I consult with a patient long distance, I also ask that he or she get an ECG from a local clinician and fax a copy of the tracing to me. I have two purposes for obtaining the ECG. First is to study the tracing for any evidence that aggressive thyroid hormone therapy is contraindicated. For example, my 12-lead electrocardiograph occasionally shows evidence of right heart damage and pulmonary hypertension in a patient who has used various weight-loss drugs. Second is to see whether the voltage of the patient’s R wave is low. If it is, increasing voltage may serve as a useful physiologic barometer of metabolic improvement.

Erfa, in a statement I quoted above, suggests that thyroid hormone therapy may reveal "occult cardiac disease." This is true and important. Rarely, thyroid hormone therapy does unveil a cardiac problem that has been obscured over time by inadequate thyroid hormone regulation of the cardiovascular system. You mentioned that you have a copy of *The Metabolic Treatment of Fibromyalgia*. I recommend that you read the section on the heart (pages 875-888), especially the subsection titled "Worsening of the Manifestations of Coronary Heart Disease" on page 877. The entire chapter is about the safe use of thyroid hormone, but it’s the heart that most practitioners are concerned about. I address those concerns and explain how to avoid adverse cardiac effects in patients using thyroid hormone. Except in the rarest cases, patients with fragile heart conditions can use thyroid hormone. But, again, caution is the key.

Erfa also mentions other precautions I strongly agree with: "Thyroid hormone therapy in patients with concomitant diabetes mellitus or insipidus or adrenal cortical insufficiency aggravates the intensity of their symptoms. Appropriate adjustments of the various therapeutic measures directed at these concomitant endocrine diseases are required."

Diabetes: I ask my patients to check their blood sugar regulation in two ways: (1) by taking several random measurements of their fasting blood sugar levels, and (2) by doing a 6-hour home glucose tolerance test (hGTT). These tests often show that a patient has glucose dysregulation. Some have fasting or reactive hypoglycemia, but most, in my clinical experience, have glucose intolerance.

In either case, too little glucose reaching a patient’s cells can cause what I view as an energy crisis. This occurs when thyroid hormone therapy accelerates intracellular energy metabolism by increasing a wide range of enzymes, but the increased energy demand conflicts with too little energy substrate in the form of glucose. Clinicians and patients often misinterpret the resulting symptoms as thyrotoxicosis. In fact, glucose dysregulation is the primary source of the symptoms. And the symptoms block the patient from using a fully therapeutic dosage of thyroid hormone.

Cortisol Deficiency: I recommend salivary testing for ruling out a cortisol deficiency. Bear in mind, though, that if a patient's liver is underregulated by thyroid hormone, it may not clear cortisol from the body at a normal rate. The person's adrenal cortices are producing too little cortisol, but the slowed liver clearance leaves the body fluids with a reference range concentration of cortisol. But as thyroid hormone increases the patient's liver clearance of cortisol to a normal rate, the patient begins to develop cortisol deficiency symptoms. In this case, thyroid hormone therapy has unveiled an adrenocortical insufficiency. This phenomenon is similar to thyroid hormone therapy unveiling an occult cardiac disorder, which I mentioned above.

The precautions Erfa recommends are indeed important ones. However, in addition to those precautions, I also ask my patients to take two other precautions; that is, to exercise and take nutritional supplements.

Exercise: I ask my patients to regularly engage in stretching, resistance, and cardiovascular exercise to tolerance. Some patients have especially low cardiovascular and muscular fitness. Despite their low muscle fitness, their muscles tend to be chronically too tight. Most of these patients must begin exercise with baby steps, increasing the intensity of their workouts only after light exercise and thyroid hormone therapy increase their tolerance for the three types of exercise.

Stretching is helpful in temporarily reducing the excess muscle tightness caused by low muscle energy from too little thyroid hormone regulation. Muscle bulking exercise is important because lean body mass is the only factor that increases the resting metabolic rate more than does thyroid hormone. And aerobic exercise gradually increases the patient's level of cardiovascular fitness. This makes the heart more resistant to adverse effects from a dosage of thyroid hormone high enough to enable the patient to get well.

Nutritional Supplements: Next, I ask each patient to take a wide array of nutritional supplements, especially B complex vitamins. The importance of this can hardly be overemphasized.

If a patient hasn't been taking supplements, he or she may have borderline nutritional deficiencies. Many micronutrients function in cells as coenzymes. Thyroid hormone increases the production of many enzymes, causing a faster expenditure of their micronutrient coenzymes. When a patient doesn't take nutritional supplements, as thyroid hormone accelerates his or her metabolic rate, borderline nutritional inadequacies may become severe deficiencies. A deficiency of some B complex vitamins, calcium, or magnesium can cause nervous system and muscle hyperirritability. Clinicians and patients may mistakenly believe that too much thyroid hormone is at fault. In fact, the patient isn't even taking a fully therapeutic dosage of thyroid hormone.

A particularly harmful nutritional deficiency involves depletion of vitamin B1 from accelerated energy metabolism caused by thyroid hormone. The patient must regularly take in enough vitamin B1 to compensate for its increased intracellular expenditure. If he or she doesn't, a resulting B1 deficiency can cause beriberi-type cardiomyopathy—even though he or she is still taking too little thyroid hormone to recover from the hypothyroid symptoms.

This set of precautions and recommendations are the base from which I operate to ensure my patients' safety during thyroid hormone therapy. Keeping the precautions and recommendations in mind can make thyroid hormone therapy with a T4/T3 product or T3 alone truly effective. It can also provide your patients with the safety you're admirably concerned about. If you learn of other precautions that clinicians should be aware of, we'll be happy if you'll share them with the readers and staff of *Thyroid Science*. I wish you the most rewarding and prosperous sailing with natural medicine.

Cordially,
Dr. John C. Lowe
Editor-in-Chief
Thyroid Science

August 4, 2008

From the Editors:

We have just received notice that Thyroid UK, the thyroid patient advocacy organization in the United Kingdom, has officially received charity status. Thyroid UK has been working towards registered charity status for some time and after a lot of work, they have now achieved this.

Thyroid UK's objects are the relief of sickness of people suffering from thyroid disease and related illnesses, for the benefit of the public. To this end, those who work through Thyroid UK provide a number of humanitarian services. These include disseminating information and support to sufferers of thyroid disease; promoting public awareness of thyroid disorders; acting as a informational resource center; encouraging scientific research for the education, alleviation, care, treatment and cure of thyroid disease; and raising funds needed to achieve their objectives.

Lyn Mynott is Chief Executive of the organization. "Achieving registered charity status," she said, "will mean that we will be seen as a more professional organization and also that more funds will become available to us to achieve our objects."

Thyroid UK was recently been chosen by the Department of Health from over 120 applications to participate in the testing phase of a new scheme to ensure good quality information across the health and social care sector. Thyroid UK is the second largest thyroid charity in the UK and is an independent organization. It is run by patients for patients.

Dr. John C. Lowe, Editor-in-Chief of *Thyroid Science*, is proud to be a member of the Board of Medical Advisors of Thyroid UK. "Part of pride in being involved with Thyroid UK is the affiliation with Lyn Mynott. After being ill for 15 years and without knowing what was wrong, she had a thyroidectomy and treatment with thyroxine. This enabled her to regain her health. Lyn then began to campaign for better treatment, and she started a small support group that met in her living room. After appearing on BBC Watchdog Healthcheck in 1999, she was inundated with emails and phone calls. This spurred her on to set up Thyroid UK.

Thyroid UK's Contact Information: Tel: 01255 821733 Fax: 01255 820407
enquiries@thyroiduk.org www.thyroiduk.org

Subject: About *Thyroid Science*
From: Anonymous Reader
Date: Thu, June 19, 2008 10:21 am
To: Editor@thyroidscience.com

Dear Editor: I have been taking Eltroxin then later Synthroid since 1974. I discovered *Thyroid Science* just today. It is apparently a new publication? I would like information regarding the journal. Thank you

Dear Reader: *Thyroid Science* is an open-access electronic journal started a couple of
years ago by Dr. John C. Lowe's publisher, McDowell Publishing Company, LLC. It is committed to providing a publishing outlet for scientifically-oriented patients, clinicians, and researchers whose writings are usually censored by conventional endocrinology journals. The latter journals usually publish only papers that, as Dr. Lowe says, favor the financial interests of the drug companies that advertise in the journals. For all practical purposes, he says, those journals are ruled by advertising drug companies with the complicity of the

endocrinology specialty. In contrast to those journals, *Thyroid Science* is dedicated to publishing papers without censoring their content to facilitate commercial interests. You are welcome to read anything published in *Thyroid Science*, and, if you wish, to contribute to the journal. I hope this answers your question.

Sincerely,
Tracy Majors
Assistant Editor
Thyroid Science (www.ThyroidScience.com)

Subject: Fine-needle aspiration and thyroid hormone resistance
Date: February 23, 2008
To: Editor@ThyroidScience.com
From: peter.warmingham@whsmithnet.co.uk

Dear Dr. Lowe: Are you aware of the paper by E Tjørve, KMC Tjørve, JO Olsen, R Senum, H Oftebro titled "On commmonness and rarity of thyroid hormone resistance: A discussion based on mechanisms of reduced sensitivity in peripheral tissues" (*Medical Hypotheses*, (2007) 69, 913-921)? In it the authors call for a test for peripheral resistance. Since the standard thyroid function blood tests don't serve this purpose. which of course the standard thyroid function blood tests don't. Maybe the fine-needle aspiration (FNA) technique used by Dr Bo Wikland and his colleagues would fit the bill?

Peter Warmingham, Thyroid UK Committee

Dear Peter: I have read the E Tjørve paper. I was pleased that Dr. Tjørve and his coauthors mentioned measuring the basal metabolic rate as a method for testing for resistance. I have used the test in my clinical practice for several years and published two studies so far using the method:

Report at *Medical Science Monitor:*
http://www.medscimonit.com/abstracted.php?level=4&id_issue=40182
(When you reach the page at *Medical Science Monitor*, scroll down to the second paper under "Clinical Research".)

Report at *Thyroid Science*: http://www.thyroidscience.com/studies/lowe.2006/lowe.2nd.rmr.fms.htm

Along with Tjorve et al, I believe that the basal or resting metabolic rate measurement is most useful clinically for identifying resistance patients, at least those with peripheral resistance. (Having peripheral resistance, of course, means that a patient's pituitary gland is normally or almost normally responsive to thyroid hormone, but most tissues peripheral to the pituitary are partially resistant.) Dr. Wikland's FNA identifies patients who have autoimmune thyroiditis despite reference range antithyroid antibody levels. Most of the patients are hypothyroid, which is the reason he and his colleagues term the disorder "subchemical hypothyroidism."

Some of these patients may also have peripheral resistance. But if they improve or recover with doses of thyroid hormone that are lower than supraphysiologic amounts, that would indicate that they are only hypothyroid and not resistant.

Most thyroid hormone resistance patients have to use supraphysiologic dosages of T3 to get well. Even T4/T3 products such as Armour usually don't work for them, not unless they use huge dosages, such as 12 grains or more. I have a book published in 1962 written by an endocrinologist—an endocrinologist from the time when many of them practiced clinical medicine rather than the extremist technocratic medicine of most endocrinologists today. In the book, the endocrinologist wrote that some of his "hypothyroid" patients didn't recover until they took as much as 60 grains of desiccated thyroid per day. I assume those patients really had peripheral resistance, as that amount would contain roughly 540 mcg of T3. That's truly a supraphysiologic daily dosage!

As I have, Dr. Wikland has found that most hypothyroid patients must suppress their TSH levels before they recover. I don't know the dosages his patients typically use, but if some of them use dosages that are well into the supraphysiologic range, the patients are probably partially resistant to thyroid hormone.

I use the following criteria to diagnose peripheral resistance: the patient has before treatment (1) hypothyroid-like symptoms before treatment, (2) reference range TSH and thyroid hormone levels, and (3) an abnormally low resting metabolic rate; and after treatment, he or she (4) recovers from his or her symptoms with a supraphysiologic dosage of plain T3 (5) with no evidence of thyrotoxicosis.

There are laboratory methods for testing for resistance. For example, we can use fibroblasts from a patient’s skin. If a supraphysiologic amount of T3 is needed to inhibit the fibroblasts' synthesis and secretion of connective tissue constituents such as fibronectin, then the patient's cells (at least his or her fibroblasts) are resistant to thyroid hormone. I don’t use this particular test for two reasons: first, it isn't available commercially; and second, even if it was, it requires a painful punch biopsy of the skin that I would prefer not to subject patients to.

To sum up, Dr. Wikland's FNA can certainly identify patients who are hypothyroid due to autoimmune thyroiditis. However, the procedure would not identify or rule out peripheral resistance to thyroid hormone.

Sincerely,
Dr. John C. Lowe
Editor-in-Chief
Thyroid Science

Subject: Re: *Thyroid Science*: Jan. 18, 2008, New Publications
Date: Fri, January 18, 2008 4:53 pm
To: Editor@ThyroidScience.com

Dear Dr. Lowe: Dr. Bo Wikland's paper (regarding treating euthyroid Hashimoto's patients with thyroxine) is unbelievably timely. I am seeing my doctor for the first time in over a month. I will be getting the results from my last full thyroid panel and hope to see a lowered antibody count.

I recently dosed up to 120mg of Armour and remained on the dose for three weeks prior to testing. At this point I need to bring my doctor up to date on what I've been trying to accomplish. I'm now up to 150mg of Armour and with the addition of Cortef to my program believe I may be beginning to get the improvement that I hoped for.

As my doctor views me as a "euthyroid Hashimoto's patient," it will be helpful to come armed with research as I try to get him onboard with my current strategy. My doctor and I have a good working relationship, and we go back many years. He's a long standing alternative doc and a good listener—so I am cautiously optimistic that all will go well. Thank you again for all that you, Tammy, and your staff do. Regards . . .

Dear Chris: I hope you're doctor responded well to Dr. Wikland’s paper. One of our purposes at *ThyroidScience*.com is to provide patients like you with publications by experts in the thyroid field whose publications are often truncated and placed in inconspicuous places in endocrinology journals, or rejected for publication altogether to avoid offending the journals' advertisers—usually ones that profit from T4-replacement therapy. I appreciate you writing. Your email lets us know that we're on the right track in publishing *ThyroidScience*.com.

Dr. John C. Lowe
Editor-in-Chief

Patient Asking Weather Thyroiditis Can Be Detected by Needle Aspiration in a

Treated Patient? *Response to editorial on Dr. Bo Wikland*'s Research on Autoimmune Thyroiditis

December 7, 2007

Dear Dr. Wikland: I was very interested to read Dr. Lowe’s editorial in Thyroid Science about "subchemical hypothyroidism," which you discovered and named. I am one of Dr Gordon Skinner's patients, and likely to get hung out to dry if the General Medical Council does its worst. I hope you can answer this for me, if you don't mind.

I was wondering whether the needle biopsy would still show anything useful in a clinically hypothyroid, but biochemically euthyroid, patient who has received treatment. I take 3.5 grains of Armour Thyroid.

Untreated, I had a TSH of 4.0 (reference range was 0.4-4.0) and a basal temp of 35 C-36.2 C (95 F-97.16 F). I was chronically fatigue for 28 years with other signs and symptoms (except I had normal reflexes for some reason). I had 'normal' levels of thyroid antibodies.

I cannot get treatment under our UK National Health System, as I can from Dr Skinner, because my TSH is now undetectable and my original need for thyroid replacement denied. So if this method would still show anything now (without my having to come off the Armour to satisfy anyone's curiosity now as to my untreated status), I would be very grateful to know. Dr Skinner is a bit busy just now, poor man.

Thank you and best wishes,
UK patient

Dear Belinda: Thank for your inquiry. I understand that you have achieved wellness on Armour Thyroid, but fear that you might be denied continued treatment in the UK because your TSH level is undetectable.

Having a desirable TSH level when on supplementary treatment with thyroid hormone is a hot potato. Mainstream opinion advocates "restoring TSH levels to normal," irrespective of patients' response to the treatment needed to achieve this. This is a *theoretical* point of view, which, when confronted with the patient’s unsatisfactory response, very often proves to be wrong.

Our rationale for thyroid hormone replacement in autoimmune thyroid disease when the patient has symptoms of hypothyroidism is not to correct the hormone deficiency—the levels of circulating hormone, free T4 and free T3 are, usually appear normal. Rather, our intention with hormone supplementation is to mitigate autoimmune activity. Our hypothesis is that the TSH in this context is detrimental in promoting autoimmune activity. Therefore many (but not all) patients require a low level of TSH.

It is very unfortunate that patients requiring "suppressive" doses of thyroid hormone are denied adequate treatment. Patients are the best judges of their own health.

In the UK, there is one highly respected specialist, Dr. Anthony Toft, who advocates a flexible approach in managing treatment with thyroid hormone.[1] Fortunately, in Sweden where I practice, some clinical pathologists comment approvingly on a "suppressed" TSH that it is compatible with adequate supplementation.

I sincerely hope that you will be allowed the dose of thyroid hormone you require.

Reference

1. Toft, A.: Thyroid, 15:124-126. 2005.

Best wishes,
Bo Wikland, MD
Hötorget Medical Center
Sveavägen 13
SE-111 57 Stockholm, Sweden

Letters in Response to Dr. Lowe's Critique: Thyroid Hormone Replacement Therapies: Ineffective and Harmful for Many Hypothyroid Patients

On June 19, 2004, Dr. John Dommisse sent an email to Dr. Lowe in response to his critique of the replacement studies. Dr. Dommisse is a physician who practices nutritional, metabolic, and psychiatric medicine, and who hosts a popular telemedicine website. He is a member of the Endocrine Society, which publishes the *Journal of Clinical Endocrinology and Metabolism* (*JCEM*). *JCEM* published two of the replacement studies in 2003, and an editorial in which the authors reiterated the invalid conclusion of the endocrinologists who conducted the studies.

Dr. Dommisse's email included a copy of a letter he'd written to the Editor of *JCEM*. He wrote the letter in response to the reports of the replacement studies. *JCEM* declined to publish his letter, so he gave Dr. Lowe permission to publish it here as support for Dr. Lowe's critique.

In his email to Dr. Lowe, Dr. Dommisse wrote, "*JCEM* would not even publish a (longish, admittedly) LETTER that I wrote to the editor in response to that spate of bogus articles!"[1]

Dr. Lowe replied:

> I am not surprised that *JCEM* didn't publish your letter. I'm not surprised despite your letter's precise relevancy to the articles about the replacement studies, despite the excellent points you raised about treatment and avoiding adverse effects, and despite your clear prose. We became convinced long ago that, regarding the diagnosis and treatment of hypothyroidism, most major medical journals are not published in the pursuit of truth. If they were, they would provide for debate of dissenting views—as is traditional in real sciences. Instead, in our view, the purpose of the journals, in regard to the diagnosis and treatment of hypothyroidism, is to perpetuate medical acceptance of financially profitable beliefs and to censor dissenting views that might threaten financial markets nourished by those beliefs. What bothers me most is that, in my opinion, to serve those two purposes, those who decide what will and won't be published in those journals must carry on with cavalier disregard for the pernicious impact of those beliefs on humanity.[2]

Dr. Dommisse's full letter to the Editor of the *Journal of Clinical Endocrinology and Metabolism*

References

1. Dommisse, J.: Personal written communication with Dr. John C. Lowe. June 19, 2004.
2. Lowe, J.C.: Personal written communication with Dr. John Dommisse. June 19, 2004.

Subj: Brief Comment on Critique of Thyroid Hormone Replacement Studies
Date: 6/8/2004 4:47 PM Mountain Daylight Time
From: piek@waitrose.com
To: drlowe@drlowe.com
Sent from the Internet

Dear Editor: The original Bunevicius research found benefits for T3/T4 over T4 and was followed up by a further analysis (*Int. J. Neuropsycopharmacology*, 2000, 3:167-174) which demonstrated that these benefits applied only to those on TSH-suppressive doses of thyroid hormones, particularly for thyroid cancer. Each of the four replacement studies tested patients on lower doses.

However, "Combined Thyroxine/Liothyronine [T4/T3] Treatment Does Not Improve Well-Being, Quality of Life, or Cognitive Function Compared to Thyroxine Alone: A Randomized Controlled Trial in Patients with Primary Hypothyroidism" (Walsh et al. *JCEM* 88(10):4543-4550) is a classic. ". . . subjects attended after an overnight fast and before taking T4 or study medication (i.e. 24 h after the previous dose)." Their data shows that the T3/T4 group had lower T3 levels than the T4 group and in the Discussion section they acknowledge the 24-hour half life of T3! Duh!!! Jim Harwood.

piek@waitrose.com

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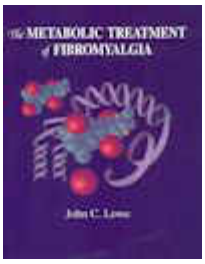

The Metabolic Treatment of Fibromyalgia
by Dr. John C. Lowe
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SPECIAL ANNOUNCEMENT
from the **Center for Metabolic Health, LLC**
and the **Fibromyalgia Research Foundation**
Newsletter, August 26, 2006

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Two New Studies Show that Fibromyalgia Patients Have Low Metabolic Rates and Low Basal Temperatures

These Studies, Along with Other Evidence, Now Confirm the Major Cause of Fibromyalgia

Twelve years ago, Dr. John C. Lowe and his research team hypothesized that fibromyalgia patients have abnormally low metabolism. They also hypothesized that the main cause of the low metabolism is too little thyroid hormone regulation of patients’ bodies and brains. Nine years ago, the researchers conducted double-blind studies showing that thyroid hormone therapy could relieve fibromyalgia patients’ symptoms. This strongly suggested that the patients do have low metabolism.

Now, two new studies confirm that the researchers were correct. A team from the Fibromyalgia Research Foundation found that female fibromyalgia patients had severely low resting metabolic rates and abnormally low basal body temperatures compared to matched healthy controls.

The *Medical Science Monitor*, a major international journal for experimental medicine, published the first study in early July. The second study was published today in *Thyroid Science*, a new electronic journal. Each journal provides free access online to the full text of the reports.

The research team from the Fibromyalgia Research Foundation included Dr. Lowe, Dr. Gina S. Honeyman, and Jackie Yellin. Richard Garrison, MD and Jane Jones, RN helped facilitate the study in various ways. Most importantly, those who gave tax-deductible donations to the Foundation made the study possible.

According to Dr. Lowe, "It’s now time for fibromyalgia researchers, treating doctors, and patient advocates to face the irrefutable facts and focus on inadequate thyroid hormone regulation as the main cause of fibromyalgia symptoms. Of course, some doctors will say, ‘I just don’t believe in that.’ This is predictable, but it’s also distinctly unscientific and unbecoming a rational mind. When overwhelming scientific by Dr. Gina Honeyman-Lowe & Dr. John C. Lowe

evidence dictates, there's only one reasonable and humanitarian course of action for a doctor: to open-mindedly change his or her mistaken ideas and put to use the new, scientifically-confirmed beliefs for the welfare of patients."

Dr. Honeyman commented, "The results of the two studies, combined with an abundance of other evidence, show that hypothyroidism and/or thyroid hormone resistance are the main mechanisms of fibromyalgia. In my clinical work with these patients for the past ten years I've helped them fully recover or significantly improve with a treatment protocol based on this hypothesis." Dr. Lowe added: "I'm confident that no one in the field of fibromyalgia can refute the conclusion that we've solved the problem. The evidence is now simply overwhelming that we were right all along."

Jackie Yellin pointed out that the huge body of evidence supporting these hypotheses is comprehensively summarized in the introduction to the report published in *Thyroid Science*. She urges all who are interested in fibromyalgia to read the introduction and conclusion to this second report. "The journal is generous," she said, "in letting us present all the evidence that inadequate thyroid hormone regulation is the main cause of what we call 'fibromyalgia.'"

Patients who want their doctors to treat them with thyroid hormone should print both reports. The reports should enable doctors to understand the reasons that thyroid hormone therapy is essential for most patients to recover from their fibromyalgia symptoms. In addition, a massive amount of information on www.drlowe.com elaborates on the hypotheses and the evidence showing that the hypotheses are correct.

Report at *Medical Science Monitor:*

http://www.medscimonit.com/abstracted.php?level=4&id_issue=40182

When you reach the page at *Medical Science Monitor*, scroll down to the second paper under "Clinical Research".

Report at *Thyroid Science*: http://www.thyroidscience.com/studies/lowe.2006/lowe.2nd.rmr.fms.htm

Clinical Care

To inquire about long-distance consulting services or treatment at the Center for Metabolic Health, please contact Bethany Bushman. You can reach her by e-mail at Tammy@drlowe.com, or by telephone at (603) 391-6061.

Sponsored by,
Dr. John C. Lowe & Dr. Gina S. Honeyman
1800 30th Street, Suite 216, Boulder, CO 80301 USA
Tel (603) 391-6061 Fax (303) 496-6200 Tammy@drlowe.com

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Follow-up Questions about Dr. Lowe's Own Thyroid Story: His Answers

Where to Buy Inexpensive Quality Nutritional Supplments

Tammy Lowe

Over the years, Dr. Lowe and I have spent a king's ransom on nutritional supplements. We bought most of them at local health food stores and pharmacies.

When he was a licensed clinician, he could buy dietary supplements and nutraceuticals from companies that marketed them only to health care professionals. The companies, of course, gave practitioners discounts so that they could sell the products to their patients for a profit. Except for one year in clinical practice, 1979, he seldom bought from these companies. Why?

"One reason," Dr. Lowe said, "is that some patients who consulted me had stopped taking nutritional supplements. When I asked them why, they told me something that bothered me: 'I just can't afford them,' they said."

"When I asked why they didn't buy less expensive supplements than the ones their doctors sold, their answer bothered me even more.'My doctor told me,' they said, 'that *only* the supplements he sold were effective. He said the supplements you can buy in stores weren't effect and were a waste of money. But his supplements were so expensive that I just couldn't buy them anymore. Since the supplements in stores weren't effective, I just stopped taking supplements altogether.'"

"Some companies such as Metagenics," Dr. Lowe said, "which doctors' sell to patients charged what he considers to be obscene prices for most of their supplements. The doctors and Metegenics make a financial killing of the products. For example," he said, "several years ago, I knew an osteopathic physician in Michigan who took in some $40,000 each month by selling Metagenic products to her patients.

At that time, I was close friends with a brilliant young chiropractic physician, Dr. Nick Calvino. At the time, Nick worked for Metagenics, selling the company's products to practicing MDs, DCs, and DOs. Nick was patient-oriented, and he was as ethical as physicians come. "It sickens me sometimes," he told me, "to have to babble to docs the Metagenics marketing crap: that is, that Metagenics products are in all kinds of ways superior to dietary supplements available through other companies and in stores."

Nick ranks among the most knowledgeable physicians I've every known. Whatever he was involved in, he extensively studied it, and he knew as much about it as any other human alive. And that includes nutritional supplements. It was clear to me that his knowledge of nutrition put him at odds with Metagenics. I listened when he told me, 'Metagenics products are really no different from what patients can buy online for a fraction of the cost.' That pained Nick and it pained me that his high ethical standard was compromised by pandering Metagenics products to practicing clinicians.

Nick Calvino

Dr. Nick Calvino

Nick didn't last long at Metagenics, despite the fact that I wrote a letter of praise and endorsement to the President of the company, biochemist Jeffery Bland. I assume Bland failed to recognize Nick's brilliance. Not long afterward, he left the company.

In trying to convince clinicians that Metagenics products were somehow superior to those of other companies, Nick felt he was being disingenuous. This clashed with his extremely high ethical standard, and he told me that he couldn't keep at that job and live with himself.

I was heartbroken when, not long after, I learned from Nick's stepmother, an ER physician, that he had killed himself. Of course, I'm in no way attributing Nick's suicide to Metagenics and their sales programs. More was involved. For example, I don't believe he could unconditionally accept so much about life. For example, Nick was being severely disillusioned and outraged by the contrast between being a chiropractic physician and the lies he was told about that professional status on "career day" before he began college at the Cleveland Chiropractic College. He was a member of a group of students who sued the College for misrepresenting the scope of practice of chiropractic doctors. But because Nick, in his brilliance, knew so much about nutritional supplements, he was especially upset about all the hype that misleads people into spending far more money than necessary on supplements.

The point I'm making in quoting Dr. Lowe here is this: You don't have

Bette Dowdell Publishes Dr. Lowe's Detailed Answers to Follow-up Questions about His Own Thyroid Story

Tammy Lowe

Bette Dowdell

Today, our friend and colleague Better Dowdell has published Dr. Lowe's answers to follow up questions to her interview with him about his personal thyroid history. Link to interview: http://instantteleseminar.com/?eventid=14918178.

During Bette's interview with Dr. Lowe, time was too short for Dr. Lowe to answer many attendees' questions. Bette asked Dr. Lowe to answer these questions, and he happily agreed. Bette has now published them as written Q&As. Her link to the Q&As is below: http://toopoopedtoparticipate.com/blog/dr-john-c-lowe-speaks/

We've received many positive responses to Dr. Lowe sharing his own thyroid history. Some have written to us and said they took great solace hearing Dr. Lowe talk about his family and personal history of depression and cognitive dysfunction. And they were especially intrigued in hearing how he recovered with T3 therapy 25 years ago.

"I say I recovered 25 years ago with T3. By that I mean that I don't have the deep suicidal depression and severely poor mental function I had before then. Some times I let melancholy go too far, and I depress myself. The depression, however, isn't the horrific kind I suffered from before beginning T3 therapy. But it's depression nonetheless. I let melancholy progress to depression by foolishly interpreting some situation as hopeless, awful, and unbearable. For example, I sometimes—for several hours—come to this irrational conclusion regarding the endocrinology specialty's chokehold on hypothyroid patients. But when I recognize that I'm depressed, I vigorously dispute my irrational conclusion. For example, I remind myself that the situation is *not* hopeless. There's evidence that it's not. For example, more researchers are publishing studies that refute the T4-replacement nonsense. And the older endocrinologists who ruined the lives of millions of patients with T4 replacement are courteously retiring and dying. Once all of them are gone, a new humane endocrinology specialty will come to reign."

Dr. Lowe also wrote, "I have occasionally had some mild cognitive dysfunction in the last 25 years. But that's mainly resulted from a lack of deep, restful sleep. I'm highly strategic in seeing to it that I get enough sleep to have a sharp cognitive edge. I do this especially when I'm working through a research project or involved in a written debate."

Links to Bette's Posting of Dr. Lowe's Answers to Followup Questions: http://toopoopedtoparticipate.com/blog/dr-john-c-lowe-speaks/

Bette Dowdell's Free Recorded Interviews with Dr. Lowe:

Sept. 14, 2010 teleseminar: http://attendthisevent.com/?eventid=12945333

Bette and Dr. Lowe's recorded conversation about his own thyroid story (Dec. 29, 2010): http://instantteleseminar.com/?eventid=14918178

Sign up to receive Bette's weekly ezine: http://toopoopedtoparticipate.com/

We encourage our clients to read Bette's electronic book, *Pep for the Pooped: The Vitamins And Minerals Your Body Is Starving For* (Glendale AZ Oct. 14, 2009)

Consultations with Bette. Dr. Lowe strongly recommends that patients consult with Bette Dowdell by phone. "She's been '*there*,'" he says, "and she learned how to get herself out of there and back to a healthy, happy life. In my view, we have no better tutors and guides than people, such as Bette, who've suffered and then recovered, for they know the pathway back to health. Bette's knowledge, her wisdom, and her rarely delightful wit make her one of my favorite tutors and guides. I enthusiastically recommend consultations with this very special human being." Details at Consult With Bette.

Your doctor won't order the tests you want?

Then order the tests yourself. *In fact, order* ***any*** *lab test you want at discounted fees through our portal at* to give up nutritional supplements because you can't afford ones that are high priced. You can buy *most* supplements inexpensively now days.

Inexpensive Supplements. The cost of some supplements can't be lowered beyond a certain amount. To lower them further would make it unprofitable to provide them. This is true of the nutraceuticals at ThyroidScience.us.

The gold standard among dietary desiccated thyroid products.

Franconia Nutraceuticals

Thyro-Gold, for example, consists of the finest thyroid powder Franconia's sourcing people have been able to find. That's also true of the forskolin it contains. Our organic raw foods multi supplement is expensive to produce, but we've priced it as low as possible to make it available for you.

You can buy most other dietary/nutritional supplements at amazingly low prices. Below are the three companies from which I currently purchase most of the supplements Dr. Lowe and I take. They provide the various supplements essential for us at truly exceptionally low prices. We hope this is helpful to you.

www.directlabs.com/drlowe.

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Our Educational Consulting Service

We provide educational consulting to both patients and clinicians. Phone us at 603-391-6061, or preferably, write to us at Tammy@drlowe.com. Our Efax number is 303-496-6200. ***—Tammy Lowe***

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Tammy Lowe

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Dr. John C. Lowe, LLC
Metabolic Research & Consulting
for Patients and Clinicians

Dr. Joseph Mercola Interviews Dr. Lowe

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| Bette Dowdell starts basic training for self-care patients |

| Please sign up *anonymously* |

Please Sign Up *Anonymously*

Today, it's been some forty years that the endocrinology specialty has promoted—utterly without reasonable compromise—T4 replacement as the only safe and effective thyroid hormone therapy. Most clinicians in other specialties (say internal medicine) have had the best of intentions in restricted their hypothyroid patients to T4 replacement.

After all, these other specialist trust that the endocrinology specialty has objective considered the scientific evidence and established that, indeed, T4 replacement is the safest and most effective approach to thyroid hormone therapy.

These other clinicians have based their use only of T4 replacement on the presumption that the endocrinology specialty has been scientifically and ethically responsible. Because of this, clinicians have handcuffed their patients to T4 replacement, while trying to soften the frustrations and pains of the cuffs with soft assurances that T4 replacement is without question the best option for therapy.

Some clinicians pad the cuffs even thicker with the assurance that T4 replacement is the *only* safe and efficacious treatment.

It's no secrete that today, the endocrinology specialty has its heels dug in. It tenacious and rigidly promotes T4 replacement and uses of the TSH test as the only legitimate method for diagnosing and treating patients as having hypothyroidism.

The time for liberation from this commercially-based endorsement of T4 replacement has come. The shackling chains can soon be broken and patients freed of the horrors that T4 replacement has imposed on so many of them.

Steps are being taken that can bring about that liberation. But we need just a little help from you. Some of us stand on the front line ready to lock horns with the endocrinology specialty and its corporation sponsors. All we need from you is this: to know know that you stand back at a distance but lend us your moral support.

Quick and Simple Sign Up. Let us know you support our efforts by simply signing up at both of the websites in the box below. Your sign-up will be entirely *anonymous*.

By merely signing up, and perhaps assisting in other simple ways in the future, you can help, as Janie Bowthorpe has says, "*stop the "thyroid madness*."

Below, I've given a brief description of the two sites where you can sign up. You can, of course, get details by reading the sites themselves.

Please sign up with us. Your signing is *anonymous*. By you signing up, we'll know roughly how many people can be counted on at the time of reckoning with the endocrinology specialty and it corporation sponsors. Please sign up at each of the two sites below:

worldthyroidregister.com

tpa-uk.org.uk/register_of_counterexamples.php

(1) Sign up at the website of Gordon Skinner, eminent UK virologist. Dr. Skinner studied fibromyalgia/chronic fatigue and learned that instead of a viral infection, the condition(s) was caused by too little thyroid hormone regulation.

Dr. Skinner has courageously stood tall while being persecuted by the UK's wicked General Medical Council (GMC). The GMC is a UK agency that *presumably* protects the UK population from unfit physicians. Too often, however, it serves as a thug organization to shamelessly punish clinicians who acquire reputations for rescuing patients whose lives have been ruined T4 replacement. By signing up with your email address at Dr. Skinner's website, you'll be letting us know that you oppose the life-ruining atrocities of the Endo/Corp Cartel, the GMC, and what constitutional attorney Johanthon Emord has called the "*hopelessly* corrupt FDA." The web address to Dr. Skinner's register is: worldthyroidregister.com

(2) Go to the website of The UK Charity, "Thyroid Patient Advocacy." The charity group's website is www.tpa-uk.org.uk. This charity has created a "World Register of Counterexamples to levothyroxine-only (T4) therapy."

Mercola/Lowe Interview and Downloadable Transcript

Thyroid Hormone Therapy: the Fibromyalgia Treatment that's Usually Ignored

On February 26, 2011, Mercola.com published Dr. Joseph Mercola's interview with Dr. John C. Lowe. At the interview page, readers can download and print the transcript of the audio interview. Both, of course, are free.

Your can listen to the interview by clicking on the start button below. But if you go to Dr. Mercola's website for the interview, he has a written transcript of his and my comments. The transcript can be downloaded or printed. You can reach the transcript through the link below:

Link to Dr. Mercola's and Dr. Lowe's interview:

< http://articles.mercola.com/sites/articles/archive/2011/02/26/dr-john-lowe-on-thyroid-disease-part-1.aspx >

To listen to the interview at **YouTube**: Use the following address: http://www.youtube.com/watch?v=KjFjrPcNB5o

Please note: Dr. Mercola's interview was published early in the morning on February 26. By the evening, some people who had read or listened to the interview had correctly pointed out that Dr. Mercola and Dr. Lowe didn't talk about the importance of a wholesome diet and nutritional supplements.

These people are correct, of course: the doctors didn't talk about these topics. But the publications of both doctors show that they know that a wholesome diet and nutritional supplements are crucial if hypothyroid and thyroid resistance patients (as well as most anyone else) are to improve or recover their health. Perhaps the doctors can discuss these topics in a future interview. This time around, however, the topic was the relation of what we call "fibromyalgia" to hypothyroidism and thyroid hormone resistance.

Bette Dowdell of "Too Pooped to Participate" starts her "Moving to Health" program http://www.movingtohealth.com/

Bette Dowdell has now started her educational program "Moving to Health." Her program is basic training for specific people: those who want to learn what they need to know to overcome their endocrine-based health problems.

Bette's work to help patients is a "fast-it-forward" endeavor. She overcame her endocrine-based problems, and she works diligently to help others do so, too.

As Bette writes, "Rather than dump a humongous book on you, 'Moving to Health' comes in weekly installments that make it easy to digest the information. You get 52 weeks of in-depth information to improve your health and make your days brighter. And it's all easy to understand and simple to do."

"The step-at-a-time approach," she continues, "lets me take each part of the puzzle, explain how it works, and show you how all the pieces fit together." This way, as she explains, "you can begin to read what your body's telling you."

In each of the 52 issues, Bette will include a question she's received from a reader, along with her answer. This is important, for as Bette notes: "It helps to know that others are going through the same stuff you are, and you're not some medical weirdo. Nor a hypochondriac."

Indeed! I strongly recommend Bette's "Moving to Health" program.

About Bette Dowdell
http://www.movingtohealth.com/about/

Tammy@drlowe.com

Our Educational Consulting Service

We provide educational consulting to both patients and clinicians. Phone us at 603-391-6061, or preferably, write to us at Tammy@drlowe.com. Our Efax number is 303-496-6200. —***Tammy Lowe***

You are a counterexample if (a) you’ve continued to suffer from hypothyroid symptoms while using T4-only therapy, and (b) your symptoms improved or disappeared once you switched to a thyroid hormone product containing T3.

It doesn’t matter whether the T3-containing product was synthetic or natural. The objective of this Register of Counterexamples is to draw the matter to the attention of responsible authorities throughout the world. The motive behind the charities' Register is the dire need for an urgent, unbiased reexamination of the methods for diagnosing and managing hypothyroidism.

As Sheila Turner, head of the charity, asks of you, “Please complete the 3 questions with either 'YES', 'NO' or N/A. You can do that quickly at:

tpa-uk.org.uk/register_of_counterexamples.php.

"All responses," Sheila says, "will be collated online, and your email address (if you provide one) will be used *only* to contact you at a later date should this be become necessary. All the best to you and your loved ones."

Thank you for taking the time to help us.

Yours sincerely,
Dr. John C. Lowe
Director of Research: Fibromyalgia Research Foundation
FibromyalgiaResearch.org
Editor-in-Chief: Thyroid Science
thyroidscience.com/
(603) 391-6060 (603) 391-6061
drlowe@drlowe.com Tammy@drlowe.com
www.drlowe@drlowe.com

The gold standard among
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The “Lowe” Down on Thyroid

By *Editor* Posted *March 23, 2012* In *Anxiety/Depression/Mental Health*, *Education*, *Endocrinology*

The Expert Report Interview With Dr John Lowe

Mark Swanson, ND

This segment of The Expert Report pulls no punches. My interview guest is Dr John Lowe, author of *The Metabolic Treatment of Fibromyalgia*,[1] an extraordinary and comprehensive 1100-page text, which I found to be a fascinating journey through thyroid science. His groundbreaking work makes for a compelling link between fibromyalgia and the functional disorder of thyroid hypometabolism and tissue resistance to triiodothyronine (T_3). Herein, he continues his outspoken views by taking aim directly at the endocrine establishment on thyroid metabolics and the usefulness of assessing thyroid status as now adopted under the standards of care. His extensive body of works, research, treatment discussions, and “everything thyroid” can be found on his website, www.drlowe.com.

Dr Lowe, I am very excited about this opportunity for our interview. I know that you will have a lot to share with our NDNR *colleagues. The challenge will be to capture some of your outspoken brilliance, insight, and clinical pearls as one of the leading functional and authoritative thyroid intellects. Our ears and eyes are open, and we are taking notes. Try to keep it short, but don’t leave anything out!*

What is your educational background and current position?

I received my chiropractic degree from Southern California University of Health Sciences [Whittier] in 1977. I also have an undergraduate and graduate degree in research psychology from University of West Florida [Pensacola]. I am currently the director of research at the Research Foundation in Houston, Texas. Our foundational research was in the use of T_3 in fibromyalgia patients and longer-term follow-up studies on the effects of thyroid hormone in this patient group.

Let’s start off with this quote from your website: “I learned early during the last 16 years that the endocrinology specialty’s judgment is corrupted by financial inducements from drug companies that profit from the TSH [thyrotropin] test and T_4 [thyroxine] replacement.” You’re really taking on The Endocrine Society here. Why?

The simple reason for my taking on the endocrine community is that my mission in life is to relieve as much human suffering as I can. We have long had ample research evidence that T_4 replacement simply doesn't work for and is harmful for too many patients. Consider a large community study[2] of T_4 replacement conducted in 2002 in England. Hundreds of patients from numerous clinics taking T_4 replacement were matched with other patients who were not hypothyroid and not taking thyroid hormone products. The noteworthy results of this study were 3-fold: a hair short of 50% of the hypothyroid patients on T_4 replacement still suffered from hypothyroid symptoms, they had a significantly higher incidence of 5 potentially fatal diseases associated with underregulation with thyroid hormone, and patients on T_4 replacement had to take more drugs than did the matched controls to lower hypothyroid symptoms and better control other diseases that afflicted only the hypothyroid patients.

We have many such studies that bring into question the safety and effectiveness of T_4 replacement for many hypothyroid patients. Whenever such studies are published, endocrinologists often resort to warped thinking to encourage hypothyroid patients to continuing T_4 replacement as the only preferable approach. To me, it's obvious that something other than the scientific findings drive these endocrinologists to advocate the use of only T_4 replacement, despite its lack of safety and confirmed harm.

What led you to become so passionate about the thyroid, its misconceptions, and the need for management revision?

I entered this passionate dispute for a clear-cut reason: I was overwhelmed by evidence that conventional [allopathic] endocrinologists and drug companies that profit hugely from their mutual interaction were depriving thyroid patients of good health and well-being. My own personal experiences, of course, were only a series of countless hundreds of others I observed in clinical practice. The endocrinology specialty, however, was adamant: “If you’re on T_4 replacement and still have hypothyroid-like symptoms, that proves that something else must be the cause of your symptoms.” Despite the endocrinologists’ assurances, I’ve been fully well on 150 µg of T_3 for some 25 years now. After all those years, in 2011, I had the pleasure of writing the Foreword to a book, *Recovering with T3: My Journey from Hypothyroidism to Good Health Using the T3 Thyroid Hormone*, by the British writer Paul Robinson.[3] In the book, he describes being free from hypothyroid symptoms for 10 years by using T_3 therapy alone. Keep in mind that this therapy, in the view of many endocrinologists, couldn’t possibly have helped Mr Robinson, although it dramatically did after T_4 replacement and other forms of thyroid therapy had failed him.

You research and write extensively on the inadequate thyroid hormone regulation hypothesis. What does this encompass?

The hypothesis simply says this: a wide variety of symptoms and signs that clinicians deal with are caused mainly by too little thyroid hormone regulation of cell and tissue function. Of course, one might reasonably ask, “Too little cell and tissue regulation of exactly what?” The answer to that question varies widely. Inadequate thyroid hormone regulation of different biological compounds may give rise to different symptoms and signs. The resulting symptoms and signs aren’t necessarily the same from individual to individual. This requires that clinicians stay open-minded and diverse in their approaches to differential diagnosis. This clinical approach was used widely around the turn of the 20th century by the famed Dr William Osler and his colleagues. I’ve found that studying their publications encourages the proper orientation, which many of us call “clinical medicine.”

Explain the treatment rationale of metabolic rehabilitation.

When I first devised metabolic rehabilitation, my intention was to create a diagnostic and treatment approach that resembled the systematic approaches to physical and cardiovascular rehab. I did my best to compare rehabilitating metabolic functions of patients' bodies and minds to the 2 better-known methods for rehabilitating patients: physical and cardiovascular health and well-being. In the case of metabolic rehab, the purpose was to help patients recover their full biochemical and physiological health and well-being. Our approach was to systematically correct any and all impediments to normal cellular and physiological metabolism.

What is the difference (and misconceptions) between hypothyroid and thyroid resistance?

The main misconception I hear comes from patients, although also from a few physicians. The conception usually expressed is, "I didn't get over my symptoms even after being on 1 grain of desiccated thyroid for 6 months. Does that mean I'm thyroid hormone resistant?"

Researchers have studied the 95th percentile in which most hypothyroid patients safely got well before the TSH became problematic in the early 1970s. That 95th percentile was 2 to 4 grains of desiccated thyroid, or 120 to 240 mg; in terms of the l-thyroxine, the 95th percentile was 200 to 400 mg. Partly because of these 95th percentiles, my treatment and research team traditionally hasn't considered that a patient may have partial cellular resistance to thyroid hormone except under one condition: that is, over several weeks, the patient reached 4 grains of desiccated thyroid or 400 mg of T_4 with no improvement whatever and no thyrotoxicosis. At that dosage, the typical hypothyroid patient has begun to benefit from the dosage, and some have adverse effects. But if the patient has had no improvement of thyrotoxicity, we have traditionally begun the protocol proper for patients partially resistant to thyroid hormone.

When it comes to the thyroid, it seems physicians are not listening to many of their patients. They drive the laboratory results to a desired target as primary treatment criteria and insist that is where it needs to remain for symptom improvement. Yet, this often fails to improve or eliminate the ongoing hypothyroid symptoms. How has your research helped bridge that treatment gap?

My research group and others have measured the resting metabolic rates (RMRs) of hundreds of patients; in general, we've found that in the majority of cases RMR levels don't correlate with TSH levels. The free T_4 never correlates—ever! The free T_3 does correlate weakly, but only after we've included around 100 patients in a study. This finding with the free T_3 means that it's statistically interesting but of no clinical value. The main aim of using thyroid function test results should be to normalize oxidative metabolism. That's what the RMR and basal metabolic rate (BMR) measure—the status of a patient's oxidative metabolism. But, studies show that we can't accurately tell what a patient's oxidative metabolism is from the free T_3, free T_4, or the TSH. The result of our studies is that reaching conclusions about a patient's metabolic status based on thyroid function tests is simply foolishness and almost always flat wrong. What is most worthy of note is this: as early as 1989, conventional [allopathic] endocrinologists had been avidly promoting thyroid function blood tests, without justification, as the "gold standard" of diagnosis. This was a presumption never scientifically warranted, nor is it any more today than it was in 1989.

You state that thyroid laboratory test results "are of no value in finding an effective dose." Should we throw testing out the window?

My belief is that thyroid function tests are of value only when way out of range. Studies show that when the free T_3, free T_4, and TSH are within range, or close to it, their levels vary, as Japanese researchers have written, "dramatically." Finding distinctions in the levels are, in general, a waste of time. The reason is that the levels vary statistically significantly about every 30 minutes. And, the levels don't reliably correlate at 30-minute intervals from day to day, nor from week to week.

How is thyroid resistance and rehabilitation distinguished from Wilson syndrome?

I would like to say that I'm grateful to Dr Dennis Wilson for advocating and garnering support for clinicians using T_3 rather than T_4 alone. I must emphasize, though, that based on systematic examination I cannot agree with most of Dr Wilson's positions that relate to health and thyroidology. I've known many hundreds of resistance patients who recovered with high T_3 dosages. Yet, I don't know a single one who has maintained their recovery upon lowering their T_3 dosages all or most of the way back down. Maybe some such patients exist. However, Richard Garrison, MD, of Baylor Medical College [Houston, Texas], and I spent a year diligently searching for cases and came up completely empty handed. I can't identify a single one out of the many hundreds of resistance patients I've treated over the years.

Is reverse T_3 a strong component of thyroid resistance? Should we be measuring it as routinely as is being advocated by many functional medicine labs and practitioners?

Measuring reverse T_3 has some diagnostic value in the realm of thyroid hormone resistance. It can be useful in identifying some conditions, especially those that interfere with the activity of 5'-deiodinase, the enzyme that converts T_4 into the metabolically active hormone T_3. The conditions include high mercury levels, as in some dental workers. They also include excess cortisol production during dental and surgical procedures. Say, for example, that someone acquires a permanent lock on 5'-deiodinase. This would increase the activity of 5-diodinase, resulting in excessive production of reverse T_3. As reverse T_3 appears to be metabolically inactive, this mechanism could have a devastating effect by slowing thyroid metabolism. Obviously, it would be important to identify this problem for the sake of correcting the patient's mechanism of thyroid hormone resistance.

Dr Swanson's comment: Dr Lowe suggests here that reverse T_3 elevation is a less common occurrence and is mostly limited to certain groups. This would be in disagreement with the widely held view described by Dr Dennis Wilson (Wilson syndrome) that it is a much more common finding, resulting from chronic stress and excess cortisol production. Thus, their evaluation workup, diagnostic interpretation, and therapy approach would likely be different for the same patient.

With thyroid resistance treatment, elevations in serum T_4/T_3 will often exceed the upper reference limit. Reassure us on the adverse effect and safety management of thyroid rehabilitation therapy.

Over the decades, my treatment and research team has compared the TSH, free T_4, and free T_3 with measures clearly controlled by thyroid hormone: oxidative metabolic rates, ECG [electrocardiogram] voltages, basal temperatures, Achilles reflexes speeds, daily variances of cortisol and glucose, and many other biochemical and physiological measures. What we've found is this: the TSH, free T_4, and free T_3 do not reliably predict the other measures. In fact, the thyroid test results, as Japanese researchers have confirmed, are extremely poor predictors of biochemical and physiological measures of the effects of thyroid hormone. This has understandably led to a high level of distrust in the usefulness of thyroid function test results. Among many researchers who conduct such studies, the conventional [allopathic] endocrinology specialty's trick is divulged and over. Good riddance to the harm the test results have done.

***Please update us on your landmark text* The Metabolic Treatment of Fibromyalgia[1] *and its related chapter in the* Textbook of Natural Medicine.[4]**

In 2000, McDowell Publishing Company published my textbook *The Metabolic Treatment of Fibromyalgia*.[1] In the book, I covered what I considered—and still consider!—the folly of conventional [allopathic] medical groups concerning the diagnosis and treatment of too little thyroid hormone regulation of the human body and mind. I also included what I consider the rational alternative to the irrational conventional [allopathic] view. Then, in 2005, Joseph E. Pizzorno Jr, ND, and Michael T. Murray, ND, approached me with an extraordinary offer. They asked that I write the chapter on fibromyalgia for the sagacious third edition of their *Textbook of Natural Medicine*.[4] Much to my privilege, when the fourth edition of the textbook came due, they asked that I update and revise the fibromyalgia chapter, which I happily did.

Tell us a little about your current involvement with the online journal www.ThyroidScience.com.

My publisher started *Thyroid Science*[5] at my request 6 years ago. My purpose was to provide a peer-reviewed journal of the thyroid field for clinicians, unfettered by the commercial and political motivations that dominate publications in the conventional [allopathic] endocrinology field. I've learned a great deal by reading and editing the widely diverse papers. We have an open invitation for naturopathic physicians to submit papers. There is no other discipline with which I feel a stronger brotherhood, and I wish this were shown in the pages of *Thyroid Science*.

Dr Lowe, this has been a short but fascinating insight to the understanding, evaluation, and management of human thyroid resistance. Before we close the interview, please give us one final thought and another clinical pearl from your vast thyro–treasure chest.

Clearly to me, the most important consideration is this: each clinician should understand that, by far, the free T_4, free T_3, and TSH are the most useless tests clinicians can employ in trying to identify patients who are hypothyroid or thyroid hormone resistant. These tests are little more than a 40-year-old financial enterprise, whose uselessness and harm are now scientifically too conspicuous.

Dr Swanson's closing comment: Thank you, Dr Lowe. Our *NDNR* readers will be thirsting for much more of you after this interview. I will simply direct that in-depth learning and education experience, along with the shear pleasure of reading and listening to Dr Lowe's brilliant thyroid intellect, to www.drlowe.com and to the additional references herein.[6-21] There are so many who have benefited by your research and therapy protocols. Let me be the first to nominate you to the Thyroid Hall of Fame.

Mark Swanson, ND, writes "The Expert Report" column, which is featured in *NDNR*. Dr. Swanson has over 25 years experience as chief medical advisor, research and technical consultant, and products formulations expert to leading practitioner brand supplement manufacturers. He is a former associate editor for the *American Journal of Naturopathic Medicine*, national product director, and published researcher. He is a pioneer graduate of Bastyr University, 1984. Dr. Swanson has his private practice specializing in Preventics Care and Functional Medicine, in Sequim, Washington. Contact: drmarkswanson@gmail.com

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